

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
16 January 2003 (16.01.2003)

PCT

(10) International Publication Number  
**WO 03/004030 A1**

(51) International Patent Classification<sup>7</sup>: **A61K 31/485**, 9/00, A61P 25/04

(21) International Application Number: **PCT/US02/21396**

(22) International Filing Date: 3 July 2002 (03.07.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/303,357 6 July 2001 (06.07.2001) US

60/329,445 15 October 2001 (15.10.2001) US

60/329,432 15 October 2001 (15.10.2001) US

60/329,444 15 October 2001 (15.10.2001) US

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

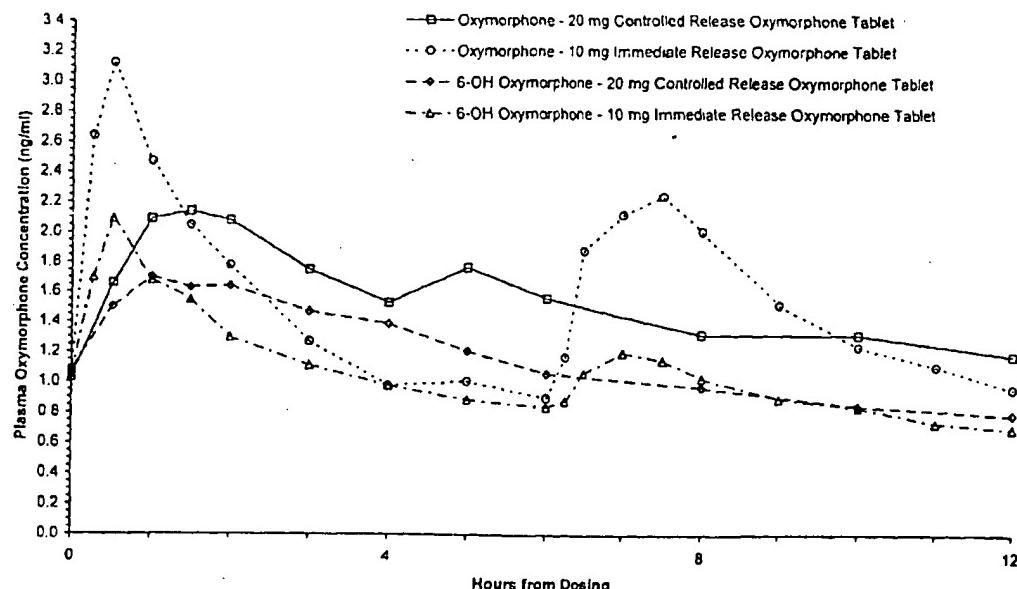
(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

[Continued on next page]

(54) Title: OXYMORPHONE CONTROLLED RELEASE FORMULATIONS



(57) Abstract: The invention pertains to a method of relieving pain by administering a controlled release pharmaceutical tablet containing oxymorphone which produces a mean minimum blood plasma level 12 to 24 hours after dosing, as well as the tablet producing the sustained pain relief.

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## OXYMORPHONE CONTROLLED RELEASE FORMULATIONS

## BACKGROUND OF THE INVENTION

Pain is the most frequently reported symptom and it is a common clinical problem which confronts the clinician. Many millions of people in the USA suffer from severe pain that, according to numerous recent reports, is chronically undertreated or inappropriately managed. The clinical usefulness of the analgesic properties of opioids has been recognized for centuries, and morphine and its derivatives have been widely employed for analgesia for decades in a variety of clinical pain states.

Oxymorphone HCl (14-hydroxydihydromorphinone hydrochloride) is a semi-synthetic phenanthrene-derivative opioid agonist, widely used in the treatment of acute and chronic pain, with analgesic efficacy comparable to other opioid analgesics. Oxymorphone is currently marketed as an injection (1 mg/ml in 1 ml ampules; 1.5 mg/ml [redacted] 1 ml ampules; 1.5 mg/ml in 10 ml multiple dose vials) for intramuscular, subcutaneous, and intravenous administration, and as 5 mg rectal suppositories. At one time, 2 mg, 5 mg and 10 mg oral immediate release (IR) tablet formulations of oxymorphone HCl were marketed. Oxymorphone HCl is metabolized principally in the liver and undergoes conjugation with glucuronic acid and reduction to 6 α- and β-hydroxy epimers.

An important goal of analgesic therapy is to achieve continuous relief of chronic pain. Regular administration of an analgesic is generally required to ensure that the next dose is given before the effects of the previous dose have worn off. Compliance with opioids increases as the required dosing frequency decreases. Non-compliance results in suboptimal pain control and poor quality of life outcomes. (Ferrell B et al. Effects of controlled-release morphine on quality of life for cancer pain. *Oncol Nur Forum* 1989;4:521-26). Scheduled, rather than "as needed" administration of opioids is currently recommended in guidelines for their use in chronic non-malignant pain. Unfortunately, evidence from prior clinical trials and clinical experience suggests that the short duration of action of immediate release oxymorphone would necessitate administration every 4-6 hours in order to maintain optimal levels of analgesia in chronic

pain. A controlled release formulation which would allow less frequent dosing of oxymorphone would be useful in pain management.

For instance, a controlled release formulation of morphine has been demonstrated to provide patients fewer interruptions in sleep, reduced dependence on caregivers, 5 improved compliance, enhanced quality of life outcomes, and increased control over the management of pain. In addition, the controlled release formulation of morphine was reported to provide more constant plasma concentration and clinical effects, less frequent peak to trough fluctuations, reduced dosing frequency, and possibly fewer side effects. (Thirlwell MP et al., Pharmacokinetics and clinical efficacy of oral morphine solution 10 and controlled-release morphine tablets in cancer patients. *Cancer* 1989; 63:2275-83; Goughnour BR et al., Analgesic response to single and multiple doses of controlled-release morphine tablets and morphine oral solution in cancer patients. *Cancer* 1989; 63:2294-97; Ferrell B. et al., Effects of controlled-release morphine on quality of life for cancer pain. *Oncol. Nur. Forum* 1989; 4:521-26.

15 There are two factors associated with the metabolism of some drugs that may present problems for their use in controlled release systems. One is the ability of the drug to induce or inhibit enzyme synthesis, which may result in a fluctuating drug blood plasma level with chronic dosing. The other is a fluctuating drug blood level due to intestinal (or other tissue) metabolism or through a hepatic first-pass effect.

20 Oxymorphone is metabolized principally in the liver, resulting in an oral bioavailability of about 10%. Evidence from clinical experience suggests that the short duration of action of immediate release oxymorphone necessitates a four hour dosing schedule to maintain optimal levels of analgesia. It would be useful to clinicians and patients alike to have controlled release dosage forms of oxymorphone to use to treat pain 25 and a method of treating pain using the dosage forms.

#### SUMMARY OF THE INVENTION

The present invention provides methods for relieving pain by administering a controlled release pharmaceutical tablet containing oxymorphone which produces at least a predetermined minimum blood plasma level for at least 12 hours after dosing, as well as 30 tablets that produce the sustained pain relief over this time period.

#### BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a pharmacokinetic profile for 6-hydroxy oxymorphone with PID scores.

Figure 2 is a pharmacokinetic profile for oxymorphone with PID scores.

Figure 3 is a pharmacokinetic profile for 6-hydroxy oxymorphone with categorical pain  
5 scores.

Figure 4 is a pharmacokinetic profile for oxymorphone with categorical pain scores.

Figure 5 is a graph of the mean blood plasma concentration of oxymorphone versus time  
for clinical study 1.

Figure 6 is a graph of the mean blood plasma concentration of oxymorphone versus time  
10 for clinical study 2.

Figure 7 is a graph of the mean blood plasma concentration of oxymorphone versus time  
for clinical study 3.

Figure 8 is a graph of the mean blood plasma concentration of 6-hydroxy oxymorphone  
versus time for clinical study 3.

15 Figure 9 is a graph of the mean blood plasma concentration of oxymorphone for  
immediate and controlled release tablets from a single dose study.

Figure 10 is a graph of the mean blood plasma concentration of oxymorphone for  
immediate and controlled release tablets from a steady state study.

#### DETAILED DESCRIPTION OF THE INVENTION

20 The present invention provides methods for alleviating pain for 12 to 24 hours  
using a single dose of a pharmaceutical composition by producing a blood plasma level  
of oxymorphone and/or 6-OH oxymorphone of at least a minimum value for at least 12  
hours or more. As used herein, the terms "6-OH oxymorphone" and "6-hydroxy  
oxymorphone" are interchangeable and refer to the analog of oxymorphone having an  
25 alcohol (hydroxy) moiety that replaces the carboxy moiety found on oxymorphone at the  
6-position.

To overcome the difficulties associated with a 4-6 hourly dosing frequency of oxymorphone, this invention provides an oxymorphone controlled release oral solid dosage form comprising a therapeutically effective amount of oxymorphone or a pharmaceutically acceptable salt of oxymorphone. It has been found that the decreased  
5 rate of release of oxymorphone from the oral controlled release formulation of this invention does not substantially decrease the bioavailability of the drug as compared to the same dose of a solution of oxymorphone administered orally. The bioavailability is sufficiently high and the release rate is such that a sufficient plasma level of oxymorphone and/or 6-OH oxymorphone is maintained to allow the controlled release  
10 dosage to be used to treat patients suffering moderate to severe pain with once or twice daily dosing. The dosing form of the present invention can also be used with thrice daily dosing.

It is critical when considering the present invention that the difference between a controlled release tablet and an immediate release formulation be fully understood. In  
15 classical terms, an immediate release formulation releases at least 80% of its active pharmaceutical ingredient within 30 minutes. With reference to the present invention, the definition of an immediate release formulation will be broadened further to include a formulation which releases more than about 80% of its active pharmaceutical ingredient within 60 minutes in a standard USP Paddle Method dissolution test at 50 rpm in 500 ml  
20 media having a pH of between 1.2 and 6.8 at 37°C. "Controlled release" formulations, as referred to herein, will then encompass any formulations which release no more than about 80% of their active pharmaceutical ingredients within 60 minutes under the same conditions.

The controlled release dosage form of this invention exhibits a dissolution rate *in*  
25 *vitro*, when measured by USP Paddle Method at 50 rpm in 500 ml media having a pH between 1.2 and 6.8 at 37°C, of about 15% to about 50% by weight oxymorphone released after 1 hour, about 45% to about 80% by weight oxymorphone released after 4 hours, and at least about 80% by weight oxymorphone released after 10 hours.

When administered orally to humans, an effective controlled release dosage form  
30 oxymorphone should exhibit the following *in vivo* characteristics: (a) peak plasma level of oxymorphone occurs within about 1 to about 8 hours after administration; (b) peak

plasma level of 6-OH oxymorphone occurs within about 1 to about 8 hours after administration; (c) duration of analgesic effect is through about 8 to about 24 hours after administration; (d) relative oxymorphone bioavailability is in the range of about 0.5 to about 1.5 compared to an orally-administered aqueous solution of oxymorphone; and (e)

5 the ratio of the area under the curve of blood plasma level vs. time for 6-OH oxymorphone compared to oxymorphone is in the range of about 0.5 to about 1.5. Of course, there is variation of these parameters among subjects, depending on the size and weight of the individual subject, the subject's age, individual metabolism differences, and other factors. Indeed, the parameters may vary in an individual from day to day.

10 Accordingly, the parameters set forth above are intended to be mean values from a sufficiently large study so as to minimize the effect of individual variation in arriving at the values. A convenient method for arriving at such values is by conducting a study in accordance with standard FDA procedures such as those employed in producing results for use in a new drug application (or abbreviated new drug application) before the FDA.

15 Any reference to mean values herein, in conjunction with desired results, refer to results from such a study, or some comparable study. Reference to mean values reported herein for studies actually conducted are arrived at using standard statistical methods as would be employed by one skilled in the art of pharmaceutical formulation and testing for regulatory approval.

20 In one specific embodiment of the controlled release matrix form of the invention, the oxymorphone or salt of oxymorphone is dispersed in a controlled release delivery system that comprises a hydrophilic material which, upon exposure to gastrointestinal fluid, forms a gel matrix that releases oxymorphone at a controlled rate. The rate of release of oxymorphone from the matrix depends on the drug's partition coefficient

25 between components of the matrix and the aqueous phase within the gastrointestinal tract. In a preferred form of this embodiment, the hydrophilic material of the controlled release delivery system comprises a mixture of a heteropolysaccharide gum and an agent capable of cross-linking the heteropolysaccharide in the presence of gastrointestinal fluid. The controlled release delivery system may also comprise a water-soluble pharmaceutical

30 diluent mixed with the hydrophilic material. Preferably, the cross-linking agent is a homopolysaccharide gum and the inert pharmaceutical diluent is a monosaccharide, a disaccharide, or a polyhydric alcohol, or a mixture thereof.

In a specific preferred embodiment, the appropriate blood plasma levels of oxymorphone and 6-hydroxy oxymorphone are achieved using oxymorphone in the form of oxymorphone hydrochloride, wherein the weight ratio of heteropolysaccharide to homopolysaccharide is in the range of about 1:3 to about 3:1, the weight ratio of heteropolysaccharide to diluent is in the range of about 1:8 to about 8:1, and the weight ratio of heteropolysaccharide to oxymorphone hydrochloride is in the range of about 10:1 to about 1:10. A preferred heteropolysaccharide is xanthan gum and a preferred homopolysaccharide is locust bean gum. The dosage form also comprises a cationic cross-linking agent and a hydrophobic polymer. In the preferred embodiment, the dosage form is a tablet containing about 5 mg to about 80 mg of oxymorphone hydrochloride. In a most preferred embodiment, the tablet contains about 20 mg oxymorphone hydrochloride.

The invention includes a method which comprises achieving appropriate blood plasma levels of drug while providing extended pain relief by administering one to three times per day to a patient suffering moderate to severe, acute or chronic pain, an oxymorphone controlled release oral solid dosage form of the invention in an amount sufficient to alleviate the pain for a period of about 8 hours to about 24 hours. This type and intensity of pain is often associated with cancer, autoimmune diseases, infections, surgical and accidental traumas and osteoarthritis.

The invention also includes a method of making an oxymorphone controlled release oral solid dosage form of the invention which comprises mixing particles of oxymorphone or a pharmaceutically acceptable salt of oxymorphone with granules comprising the controlled release delivery system, preferably followed by directly compressing the mixture to form tablets.

Pharmaceutically acceptable salts of oxymorphone which can be used in this invention include salts with the inorganic and organic acids which are commonly used to produce nontoxic salts of medicinal agents. Illustrative examples would be those salts formed by mixing oxymorphone with hydrochloric, sulfuric, nitric, phosphoric, phosphorous, hydrobromic, maleric, malic, ascorbic, citric or tartaric, pamoic, lauric, stearic, palmitic, oleic, myristic, lauryl sulfuric, naphthalenesulfonic, linoleic or linolenic acid, and the like. The hydrochloride salt is preferred.

It has now been found that 6-OH oxymorphone, which is one of the metabolites of oxymorphone may play a role in alleviating pain. When oxymorphone is ingested, part of the dosage gets into the bloodstream to provide pain relief, while another part is metabolized to 6-OH oxymorphone. This metabolite then enters the bloodstream to 5 provide further pain relief. Thus it is believed that both the oxymorphone and 6-hydroxyoxymorphone levels are important to pain relief.

The effectiveness of oxymorphone and 6-hydroxyoxymorphone at relieving pain and the pharmacokinetics of a single dose of oxymorphone were studied. The blood plasma levels of both oxymorphone and 6-hydroxyoxymorphone were measured in 10 patients after a single dose of oxymorphone was administered. Similarly, the pain levels in patients were measured after a single administration of oxymorphone to determine the effective duration of pain relief from a single dose. Figures 1-2 show the results of these tests, comparing pain levels to oxymorphone and 6-hydroxy oxymorphone levels.

For these tests, pain was measured using a Visual Analog Scale (VAS) or a 15 Categorical Scale. The VAS scales consisted of a horizontal line, 100 mm in length. The left-hand end of the scale (0 mm) was marked with the descriptor "No Pain" and the right-hand end of the scale (100 mm) was marked with the descriptor "Extreme Pain". Patients indicated their level of pain by making a vertical mark on the line. The VAS score was equal to the distance (in mm) from the left-hand end of the scale to the 20 patient's mark. For the categorical scale, patients completed the following statement, "My pain at this time is" using the scale None = 0, Mild = 1, Moderate = 2, or Severe = 3.

As can be seen from these figures, there is a correlation between pain relief and both oxymorphone and 6-hydroxyoxymorphone levels. As the blood plasma levels of oxymorphone and 6-hydroxyoxymorphone increase, pain decreases (and pain intensity 25 difference and pain relief increases). Thus, to the patient, it is the level of oxymorphone and 6-hydroxyoxymorphone in the blood plasma which is most important. Further it is these levels which dictate the efficacy of the dosage form. A dosage form which maintains a sufficiently high level of oxymorphone or 6-hydroxyoxymorphone for a longer period need not be administered frequently. Such a result is accomplished by 30 embodiments of the present invention.

The oxymorphone controlled release oral solid dosage form of this invention can be made using any of several different techniques for producing controlled release oral solid dosage forms of opioid analgesics.

In one embodiment, a core comprising oxymorphone or oxymorphone salt is  
5 coated with a controlled release film which comprises a water insoluble material and which upon exposure to gastrointestinal fluid releases oxymorphone from the core at a controlled rate. In a second embodiment, the oxymorphone or oxymorphone salt is dispersed in a controlled release delivery system that comprises a hydrophilic material which upon exposure to gastrointestinal fluid forms a gel matrix that releases  
10 oxymorphone at a controlled rate. A third embodiment is a combination of the first two: a controlled release matrix coated with a controlled release film. In a fourth embodiment the oxymorphone is incorporated into an osmotic pump. In any of these embodiments, the dosage form can be a tablet, a plurality of granules in a capsule, or other suitable form, and can contain lubricants, colorants, diluents, and other conventional ingredients.

15           Osmotic Pump

An osmotic pump comprises a shell defining an interior compartment and having an outlet passing through the shell. The interior compartment contains the active pharmaceutical ingredient. Generally the active pharmaceutical ingredient is mixed with excipients or other compositions such as a polyalkylene. The shell is generally made, at  
20 least in part, from a material (such as cellulose acetate) permeable to the liquid of the environment where the pump will be used, usually stomach acid. Once ingested, the pump operates when liquid diffuses through the shell of the pump. The liquid dissolves the composition to produce a saturated situation. As more liquid diffuses into the pump, the saturated solution containing the pharmaceutical is expelled from the pump through  
25 the outlet. This produces a nearly constant release of active ingredient, in the present case, oxymorphone.

Controlled Release Coating

In this embodiment, a core comprising oxymorphone or oxymorphone salt is coated with a controlled release film which comprises a water insoluble material. The  
30 film can be applied by spraying an aqueous dispersion of the water insoluble material

onto the core. Suitable water insoluble materials include alkyl celluloses, acrylic polymers, waxes (alone or in admixture with fatty alcohols), shellac and zein. The aqueous dispersions of alkyl celluloses and acrylic polymers preferably contain a plasticizer such as triethyl citrate, dibutyl phthalate, propylene glycol, and polyethylene glycol. The film coat can contain a water-soluble material such as polyvinylpyrrolidone (PVP) or hydroxypropylmethylcellulose (HPMC).

The core can be a granule made, for example, by wet granulation of mixed powders of oxymorphone or oxymorphone salt and a binding agent such as HPMC, or by coating an inert bead with oxymorphone or oxymorphone salt and a binding agent such as HPMC, or by spheronising mixed powders of oxymorphone or oxymorphone salt and a spheronising agent such as microcrystalline cellulose. The core can be a tablet made by compressing such granules or by compressing a powder comprising oxymorphone or oxymorphone salt.

The *in vitro* and *in vivo* release characteristics of this controlled release dosage form can be modified by using mixtures of different water insoluble and water soluble materials, using different plasticizers, varying the thickness of the controlled release film, including release-modifying agents in the coating, or by providing passageways through the coating.

#### Controlled Release Matrix

It is important in the present invention that appropriate blood plasma levels of oxymorphone and 6 hydroxy oxymorphone be achieved and maintained for sufficient time to provide pain relief to a patient for a period of 12 to 24 hours. The preferred composition for achieving and maintaining the proper blood plasma levels is a controlled-release matrix. In this embodiment, the oxymorphone or oxymorphone salt is dispersed in a controlled release delivery system that comprises a hydrophilic material (gelling agent) which upon exposure to gastrointestinal fluid forms a gel matrix that releases oxymorphone at a controlled rate. Such hydrophilic materials include gums, cellulose ethers, acrylic resins, and protein-derived materials. Suitable cellulose ethers include hydroxyalkyl celluloses and carboxyalkyl celluloses, especially hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), HPMC, and carboxy methylcellulose (CMC).

Suitable acrylic resins include polymers and copolymers of acrylic acid, methacrylic acid, methyl acrylate and methyl methacrylate. Suitable gums include heteropolysaccharide and homopolysaccharide gums, e.g., xanthan, tragacanth, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, carrageenan, and locust bean gums.

5 Preferably, the controlled release tablet of the present invention is formed from (I) a hydrophilic material comprising (a) a heteropolysaccharide; or (b) a heteropolysaccharide and a cross-linking agent capable of cross-linking said heteropolysaccharide; or (c) a mixture of (a), (b) and a polysaccharide gum; and (II) an inert pharmaceutical filler comprising up to about 80% by weight of the tablet; and (III)  
10 oxymorphone.

The term "heteropolysaccharide" as used herein is defined as a water-soluble polysaccharide containing two or more kinds of sugar units, the heteropolysaccharide having a branched or helical configuration, and having excellent water-wicking properties and immense thickening properties.

15 A preferred heteropolysaccharide is xanthan gum, which is a high molecular weight ( $>10^6$ ) heteropolysaccharide. Other preferred heteropolysaccharides include derivatives of xanthan gum, such as deacylated xanthan gum, the carboxymethyl ether, and the propylene glycol ester.

20 The cross linking agents used in the controlled release embodiment of the present invention which are capable of cross-linking with the heteropolysaccharide include homopolysaccharide gums such as the galactomannans, i.e., polysaccharides which are composed solely of mannose and galactose. Galactomannans which have higher proportions of unsubstituted mannose regions have been found to achieve more interaction with the heteropolysaccharide. Locust bean gum, which has a higher ratio of  
25 mannose to the galactose, is especially preferred as compared to other galactomannans such as guar and hydroxypropyl guar.

30 Preferably, the ratio of heteropolysaccharide to homopolysaccharide is in the range of about 1:9 to about 9:1, preferably about 1:3 to about 3:1. Most preferably, the ratio of xanthan gum to polysaccharide material (i.e., locust bean gum, etc.) is preferably about 1:1.

In addition to the hydrophilic material, the controlled release delivery system can also contain an inert pharmaceutical diluent such as a monosaccharide, a disaccharide, a polyhydric alcohol and mixtures thereof. The ratio of diluent to hydrophilic matrix-forming material is generally in the range of about 1:3 to about 3:1.

- 5       The controlled release properties of the controlled release embodiment of the present invention may be optimized when the ratio of heteropolysaccharide gum to homopolysaccharide material is about 1:1, although heteropolysaccharide gum in an amount of from about 20 to about 80% or more by weight of the heterodisperse polysaccharide material provides an acceptable slow release product. The combination of  
10      any homopolysaccharide gums known to produce a synergistic effect when exposed to aqueous solutions may be used in accordance with the present invention. It is also possible that the type of synergism which is present with regard to the gum combination of the present invention could also occur between two homogeneous or two heteropolysaccharides. Other acceptable gelling agents which may be used in the present  
15      invention include those gelling agents well-known in the art. Examples include vegetable gums such as alginates, carrageenan, pectin, guar gum, xanthan gum, modified starch, hydroxypropylmethylcellulose, methylcellulose, and other cellulosic materials such as sodium carboxymethylcellulose and hydroxypropyl cellulose. This list is not meant to be exclusive.
- 20       The combination of xanthan gum with locust bean gum with or without the other homopolysaccharide gums is an especially preferred gelling agent. The chemistry of certain of the ingredients comprising the excipients of the present invention such as xanthan gum is such that the excipients are considered to be self-buffering agents which are substantially insensitive to the solubility of the medicament and likewise insensitive  
25      to the pH changes along the length of the gastrointestinal tract.

- 30       The inert filler of the sustained release excipient preferably comprises a pharmaceutically acceptable saccharide, including a monosaccharide, a disaccharide, or a polyhydric alcohol, and/or mixtures of any of the foregoing. Examples of suitable inert pharmaceutical fillers include sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, mixtures thereof and the like. However, it is preferred that a

soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used.

The cationic cross-linking agent which is optionally used in conjunction with the controlled release embodiment of the present invention may be monovalent or 5 multivalent metal cations. The preferred salts are the inorganic salts, including various alkali metal and/or alkaline earth metal sulfates, chlorides, borates, bromides, citrates, acetates, lactates, etc. Specific examples of suitable cationic cross-linking agents include calcium sulfate, sodium chloride, potassium sulfate, sodium carbonate, lithium chloride, tripotassium phosphate, sodium borate, potassium bromide, potassium fluoride, sodium 10 bicarbonate, calcium chloride, magnesium chloride, sodium citrate, sodium acetate, calcium lactate, magnesium sulfate and sodium fluoride. Multivalent metal cations may also be utilized. However, the preferred cationic cross-linking agents are bivalent. Particularly preferred salts are calcium sulfate and sodium chloride. The cationic cross-linking agents of the present invention are added in an amount effective to obtain a 15 desirable increased gel strength due to the cross-linking of the gelling agent (e.g., the heteropolysaccharide and homopolysaccharide gums). In preferred embodiments, the cationic cross-linking agent is included in the sustained release excipient of the present invention in an amount from about 1 to about 20% by weight of the sustained release excipient, and in an amount about 0.5% to about 16% by weight of the final dosage form.

20 In the controlled release embodiments of the present invention, the sustained release excipient comprises from about 10 to about 99% by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum, from about 1 to about 20% by weight of a cationic crosslinking agent, and from about 0 to about 89% by weight of an inert pharmaceutical diluent. In other embodiments, the sustained release 25 excipient comprises from about 10 to about 75% gelling agent, from about 2 to about 15% cationic crosslinking agent, and from about 30 to about 75% inert diluent. In yet other embodiments, the sustained release excipient comprises from about 30 to about 75% gelling agent, from about 5 to about 10% cationic cross-linking agent, and from about 15 to about 65% inert diluent.

30 The sustained release excipient used in this embodiment of the present invention (with or without the optional cationic cross-linking agent) may be further modified by

incorporation of a hydrophobic material which slows the hydration of the gums without disrupting the hydrophilic matrix. This is accomplished in preferred embodiments of the present invention by granulating the sustained release excipient with the solution or dispersion of a hydrophobic material prior to the incorporation of the medicament. The 5 hydrophobic polymer may be selected from an alkylcellulose such as ethylcellulose, other hydrophobic cellulosic materials, polymers or copolymers derived from acrylic or methacrylic acid esters, copolymers of acrylic and methacrylic acid esters, zein, waxes, shellac, hydrogenated vegetable oils, and any other pharmaceutically acceptable hydrophobic material known to those skilled in the art. The amount of hydrophobic 10 material incorporated into the sustained release excipient is that which is effective to slow the hydration of the gums without disrupting the hydrophilic matrix formed upon exposure to an environmental fluid. In certain preferred embodiments of the present invention, the hydrophobic material is included in the sustained release excipient in an amount from about 1 to about 20% by weight. The solvent for the hydrophobic material 15 may be an aqueous or organic solvent, or mixtures thereof.

Examples of commercially available alkylcelluloses are Aquacoat coating (aqueous dispersion of ethylcellulose available from FMC of Philadelphia, PA) and Surelease coating (aqueous dispersion of ethylcellulose available from Colorcon of West Point, PA). Examples of commercially available acrylic polymers suitable for use as the 20 hydrophobic material include Eudragit RS and RL polymers (copolymers of acrylic and methacrylic acid esters having a low content (e.g., 1:20 or 1:40) of quaternary ammonium compounds available from Rohm America of Piscataway, NJ.).

The controlled release matrix useful in the present invention may also contain a cationic cross-linking agent such as calcium sulfate in an amount sufficient to cross-link 25 the gelling agent and increase the gel strength, and an inert hydrophobic material such as ethyl cellulose in an amount sufficient to slow the hydration of the hydrophilic material without disrupting it. Preferably, the controlled release delivery system is prepared as a pre-manufactured granulation.

## EXAMPLES

30 **Example 1**

Two controlled release delivery systems are prepared by dry blending xanthan gum, locust bean gum, calcium sulfate dehydrate, and dextrose in a high speed mixed/granulator for 3 minutes. A slurry is prepared by mixing ethyl cellulose with alcohol. While running choppers/impellers, the slurry is added to the dry blended mixture, and granulated for another 3 minutes. The granulation is then dried to a LOD (loss on drying) of less than about 10% by weight. The granulation is then milled using 5 20 mesh screen. The relative quantities of the ingredients are listed in the table below.

Table 1 - Controlled Release Delivery System

<u>Excipient</u>	<u>Formulation 1</u>	<u>Formulation 2</u>
	(%)	(%)
Locust Bean Gum, FCC	25.0	30.0
Xanthan Gum, NF	25.0	30.0
Dextrose, USP	35.0	40.0
Calcium Sulfate Dihydrate, NF	10.0	0.0
Ethylcellulose, NF	5.0	0.0
Alcohol, SD3A (Anhydrous) <sup>1</sup>	(10) <sup>1</sup>	(20.0) <sup>1</sup>
Total	100.0	100.0

1. Volatile, removed during processing

10 A series of tablets containing different amounts of oxymorphone hydrochloride were prepared using the controlled release delivery Formulation 1 shown in Table 1. The quantities of ingredients per tablet are as listed in the following table.

Table 2 - Sample Tablets of Differing Strengths

Component	Amount in Tablet (mg)				
Oxymorphone HCl, USP (mg)	5	10	20	40	80
Controlled release delivery system	160	160	160	160	160
Silicified microcrystalline cellulose, N.F.	20	20	20	20	20
Sodium stearyl fumarate, NF	2	2	2	2	2
Total weight	187	192	202	222	262
Opadry (colored)	7.48	7.68	8.08	8.88	10.48
Opadry (clear)	0.94	0.96	1.01	1.11	1.31

**Examples 2 and 3**

Two batches of 20 mg tablets were prepared as described above, using the controlled release delivery system of Formulation 1. One batch was formulated to provide relatively fast controlled release, the other batch was formulated to provide relatively slow controlled release. Compositions of the tablets are shown in the following table.

Table 3 - Slow and Fast Release Compositions

Ingredients	Example 2	Example 3	Example 4
	Slow (mg)	Fast (mg)	Fast (mg)
Oxymorphone HCl, USP	20	20	20
Controlled Release Delivery System	360	160	160
Silicified Microcrystalline Cellulose, NF	20	20	20
Sodium stearyl fumarate, NF	4	2	2
Total weight	404	202	202
Coating (color or clear)	12	12	9

The tablets of Examples 2, 3, and 4 were tested for *in vitro* release rate according to USP Procedure Drug Release USP 23. Release rate is a critical variable in attempting

to control the blood plasma levels of oxymorphone and 6-hydroxyoxymorphone in a patient. Results are shown in the following Table 4.

Table 4 - Release Rates of Slow and Fast Release Tablets

<u>Time (hr)</u>	<u>Example 2</u> <u>(Slow Release)</u>	<u>Example 3</u> <u>(Fast Release)</u>	<u>Example 4</u> <u>(Fast Release)</u>
0.5	18.8	21.3	20.1
1	27.8	32.3	31.7
2	40.5	47.4	46.9
3	50.2	58.5	57.9
4	58.1	66.9	66.3
5	64.7	73.5	74.0
6	70.2	78.6	83.1
8	79.0	86.0	92.0
10	85.3	90.6	95.8
12	89.8	93.4	97.3

## 5 Clinical Studies

Three clinical studies were conducted to assess the bioavailability (rate and extent of absorption) of oxymorphone. Study 1 addressed the relative rates of absorption of controlled release (CR) oxymorphone tablets (of Examples 2 and 3) and oral oxymorphone solution in fasted patients. Study 2 addressed the relative rates of absorption of CR oxymorphone tablets (of Examples 2 and 3) and oral oxymorphone solution in fed patients. Study 3 addressed the relative rates of absorption of CR oxymorphone tablets (of Example 4) and oral oxymorphone solution in fed and fasted patients.

The blood plasma levels set forth herein as appropriate to achieve the objects of the present invention are mean blood plasma levels. As an example, if the blood plasma level of oxymorphone in a patient 12 hours after administration of a tablet is said to be at least 0.5 ng/ml, any particular individual, may have lower blood plasma levels after 12 hours. However, the mean minimum concentration should meet the limitation set forth.

To determine mean parameters, a study should be performed with a minimum of 8 adult subjects, in a manner acceptable for filing an application for drug approval with the US Food and Drug Administration. In cases where large fluctuations are found among patients, further testing may be necessary to accurately determine mean values.

- 5 For all studies, the following procedures were followed, unless otherwise specified for a particular study.

The subjects were not to consume any alcohol-, caffeine-, or xanthine-containing foods or beverages for 24 hours prior to receiving study medication for each study period. Subjects were to be nicotine and tobacco free for at least 6 months prior to enrolling in  
10 the study. In addition, over-the-counter medications were prohibited 7 days prior to dosing and during the study. Prescription medications were not allowed 14 days prior to dosing and during the study.

#### Pharmacokinetic and Statistical Methods

The following pharmacokinetic parameters were computed from the plasma  
15 oxymorphone concentration-time data:

AUC <sub>(0-t)</sub>	Area under the drug concentration-time curve from time zero to the time of the last quantifiable concentration (C <sub>t</sub> ), calculated using linear trapezoidal summation.
AUC <sub>(0-inf)</sub>	Area under the drug concentration-time curve from time zero to infinity. AUC <sub>(0-inf)</sub> = AUC <sub>(0-t)</sub> + C <sub>t</sub> /K <sub>el</sub> , where K <sub>el</sub> is the terminal elimination rate constant.
AUC <sub>(0-24)</sub>	Partial area under the drug concentration-time curve from time zero to 24 hours.
C <sub>max</sub>	Maximum observed drug concentration.
T <sub>max</sub>	Time of the observed maximum drug concentration.
K <sub>el</sub>	Elimination rate constant based on the linear regression of the terminal linear portion of the LN(concentration) time curve.

Terminal elimination rate constants for use in the above calculations were in turn computed using linear regression of a minimum of three time points, at least two of which were consecutive.  $K_{el}$  values for which correlation coefficients were less than or equal to 0.8 were not reported in the pharmacokinetic parameter tables or included in the 5 statistical analysis. Thus  $AUC_{(0-\infty)}$  was also not reported in these cases.

A parametric (normal-theory) general linear model was applied to each of the above parameters (excluding  $T_{max}$ ), and the LN-transformed parameters  $C_{max}$ ,  $AUC_{(0-24)}$ ,  $AUC_{(0-t)}$ , and  $AUC_{(0-\infty)}$ . Initially, the analysis of variance (ANOVA) model included the following factors: treatment, sequence, subject within sequence, period, and carryover 10 effect. If carryover effect was not significant, it was dropped from the model. The sequence effect was tested using the subject within sequence mean square, and all other main effects were tested using the residual error (error mean square).

Plasma oxymorphone concentrations were listed by subject at each collection time and summarized using descriptive statistics. Pharmacokinetic parameters were also listed 15 by subject and summarized using descriptive statistics.

#### **Study 1 - Two Controlled Release Formulations; Fasted Patients**

Healthy volunteers received a single oral dose of 20mg CR oxymorphone taken with 240 ml water after a 10-hour fast. Subjects received the tablets of Example 2 (Treatment 1A) or Example 3 (Treatment 1B). Further subjects were given a single oral 20 dose of 10mg/10 ml oxymorphone solution in 180 ml apple juice followed with 60 ml water (Treatment 1C). The orally dosed solution was used to simulate an immediate release (IR) dose.

This study had a single-center, open-label, randomized, three-way crossover design using fifteen subjects. Subjects were in a fasted state following a 10-hour 25 overnight fast. There was a 14-day washout interval between the three dose administrations. The subjects were confined to the clinic during each study period. Subjects receiving Treatment 1C were confined for 18 hours and subjects receiving Treatments 1A or 1B were confined for 48 hours after dosing. Ten-milliliter blood samples were collected during each study period at the 0 hour (predose), and at 0.5, 1, 30 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, and 48 hours postdose for

subjects receiving Treatment 1A or 1B and 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 18 hours post-dose. The mean plasma concentration of oxymorphone versus time for each treatment across all subjects is shown in table 5.

Table 5 - Mean Plasma Concentration vs. Time (ng/ml)

5

Time (hr)	Treatment 1A	Treatment 1B	Treatment 1C
0	0.000	0.000	0.0000
0.25			0.9489
0.5	0.2941	0.4104	1.3016
0.75			1.3264
1	0.5016	0.7334	1.3046
1.25			1.2041
1.5	0.5951	0.8192	1.0813
1.75			0.9502
2	0.6328	0.7689	0.9055
2.5			0.7161
3	0.5743	0.7341	0.6689
4	0.5709	0.6647	0.4879
5	0.7656	0.9089	0.4184
6	0.7149	0.7782	0.3658
7	0.6334	0.6748	0.3464
8	0.5716	0.5890	0.2610
10	0.4834	0.5144	0.2028
12	0.7333	0.6801	0.2936
14	0.6271	0.6089	0.2083
16	0.4986	0.4567	0.1661
18	0.4008	0.3674	0.1368
20	0.3405	0.2970	
24	0.2736	0.2270	
28	0.3209	0.2805	
32	0.2846	0.2272	
36	0.2583	0.1903	
48	0.0975	0.0792	

The results are shown graphically in Figure 5. In both Table 5 and Figure 5, the results are normalized to a 20 mg dosage. The immediate release liquid of Treatment 1C shows a classical curve, with a high and relatively narrow peak, followed by an exponential drop in plasma concentration. However, the controlled release oxymorphone

tablets exhibit triple peaks in blood plasma concentration. The first peak occurs (on average) at around 3 hours. The second peak of the mean blood plasma concentration is higher than the first, occurring around 6-7 hours, on average).

Occasionally, in an individual, the first peak is higher than the second, although generally this is not the case. This makes it difficult to determine the time to maximum blood plasma concentration ( $T_{max}$ ) because if the first peak is higher than the second, maximum blood plasma concentration ( $C_{max}$ ) occurs much earlier (at around 3 hours) than in the usual case where the second peak is highest. Therefore, when we refer to the time to peak plasma concentration ( $T_{max}$ ) unless otherwise specified, we refer to the time to the second peak. Further, when reference is made to the second peak, we refer to the time or blood plasma concentration at the point where the blood plasma concentration begins to drop the second time. Generally, where the first peak is higher than the second, the difference in the maximum blood plasma concentration at the two peaks is small. Therefore, this difference (if any) was ignored and the reported  $C_{max}$  was the true maximum blood plasma concentration and not the concentration at the second peak.

Table 6 - Pharmacokinetic Parameters of Plasma Oxymorphone for Study 1

	Treatment 1A		Treatment 1B		Treatment 1C	
	Mean	SD	Mean	SD	Mean	SD
$C_{max}$	0.8956	0.2983	1.0362	0.3080	2.9622	1.0999
$T_{max}$	7.03	4.10	4.89	3.44	0.928	0.398
$AUC_{(0-t)}$	17.87	6.140	17.16	6.395	14.24	5.003
$AUC_{(0-inf)}$	19.87	6.382	18.96	6.908	16.99	5.830
$T_{1/2el}$	10.9	2.68	11.4	2.88	6.96	4.61

Units:  $C_{max}$  in ng/ml,  $T_{max}$  in hours, AUC in ng·hr/ml,  $T_{1/2el}$  in hours.

Relative bioavailability determinations are set forth in Tables 7 and 8. For these calculations, AUC was normalized for all treatments to a 20 mg dose.

Table 7 - Relative Bioavailability ( $F_{rel}$ ) Determination Based on  $AUC_{(0-\infty)}$ 

$F_{rel}$ (1A vs. 1C)	$F_{rel}$ (1B vs. 1C)	$F_{rel}$ (1A vs. 1B)
$1.193 \pm 0.203$	$1.121 \pm 0.211$	$1.108 \pm 0.152$

Table 8 - Relative bioavailability Determination Based on  $AUC_{(0-18)}$ 

$F_{rel}$ (1A vs. 1C)	$F_{rel}$ (1B vs. 1C)	$F_{rel}$ (1A vs. 1B)
$0.733 \pm 0.098$	$0.783 \pm 0.117$	$0.944 \pm 0.110$

**Study 2 - Two CR Formulations; Fed Patients**

Healthy volunteers received a single oral dose of 20 mg CR oxymorphone taken with 240 ml water in a fed state. Subjects received the tablets of Example 2 (Treatment 2A) or Example 3 (Treatment 2B). Further subjects were given a single oral dose of 10mg/10 ml oxymorphone solution in 180 ml apple juice followed with 60 ml water (Treatment 2C). The orally dosed solution was used to simulate an immediate release (IR) dose.

This study had a single-center, open-label, randomized, three-way crossover design using fifteen subjects. The subjects were in a fed state, after a 10-hour overnight fast followed by a standardized FDA high-fat breakfast. There was a 14-day washout interval between the three dose administrations. The subjects were confined to the clinic during each study period. Subjects receiving Treatment 2C were confined for 18 hours and subjects receiving Treatments 2A or 2B were confined for 48 hours after dosing. Ten-milliliter blood samples were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, and 48 hours postdose for subjects receiving Treatment 2A or 2B and 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 18 hours postdose. The mean plasma concentration of oxymorphone versus time for each treatment across all subjects is shown in table 9.

Table 9 - Mean Plasma Concentration vs. Time (ng/ml)

<u>Time (hr)</u>	<u>Treatment 2A</u>	<u>Treatment 2B</u>	<u>Treatment 2C</u>
0	0.000	0.000	0.0000
0.25			1.263
0.5	0.396	.0553	1.556
0.75			1.972
1	0.800	1.063	1.796
1.25			1.795
1.5	1.038	1.319	1.637
1.75			1.467
2	1.269	1.414	1.454
2.5			1.331
3	1.328	1.540	1.320
4	1.132	1.378	1.011
5	1.291	1.609	0.731
6	1.033	1.242	0.518
7	0.941	0.955	0.442
8	0.936	0.817	0.372
10	0.669	0.555	0.323
12	0.766	0.592	0.398
14	0.641	0.519	0.284
16	0.547	0.407	0.223
18	0.453	0.320	0.173
20	0.382	0.280	
24	0.315	0.254	
28	0.352	0.319	
32	0.304	0.237	
36	0.252	0.207	
48	0.104	0.077	

The results are shown graphically in Figure 6. Again, the results have been normalized to a 20 mg dosage. As with Study 1, the immediate release liquid of

Treatment 2C shows a classical curve, with a high and relatively narrow peak, followed by an exponential drop in plasma concentration, while the controlled release oxymorphone tablets exhibit triple peaks in blood plasma concentration. Thus, again when we refer to the time to peak plasma concentration ( $T_{max}$ ) unless otherwise specified,  
5 we refer to the time to the second peak.

Table 10 - Pharmacokinetic Parameters of Plasma Oxymorphone for Study 2

	Treatment 2A		Treatment 2B		Treatment 2C	
	Mean	SD	Mean	SD	Mean	SD
$C_{max}$	1.644	0.365	1.944	0.465	4.134	0.897
$T_{max}$	3.07	1.58	2.93	1.64	0.947	0.313
$AUC_{(0-t)}$	22.89	5.486	21.34	5.528	21.93	5.044
$AUC_{(0-inf)}$	25.28	5.736	23.62	5.202	24.73	6.616
$T_{1/2el}$	12.8	3.87	11.0	3.51	5.01	2.02

Units:  $C_{max}$  in ng/ml,  $T_{max}$  in hours,  $AUC$  in ng·hr/ml,  $T_{1/2el}$  in hours.

In Table 10, the  $T_{max}$  has a large standard deviation due to the two comparable peaks in blood plasma concentration. Relative bioavailability determinations are set forth  
10 in Tables 11 and 12.

Table 11 - Relative Bioavailability Determination Based on  $AUC_{(0-inf)}$

$F_{rel}$ (2A vs. 2C)	$F_{rel}$ (2B vs. 2C)	$F_{rel}$ (2A vs. 2B)
$1.052 \pm 0.187$	$0.949 \pm 0.154$	$1.148 \pm 0.250$

Table 12 - Relative bioavailability Determination Based on  $AUC(0-18)$

$F_{rel}$ (2A vs. 2C)	$F_{rel}$ (2B vs. 2C)	$F_{rel}$ (2A vs. 2B)
$0.690 \pm 0.105$	$0.694 \pm 0.124$	$1.012 \pm 0.175$

As may be seen from tables 5 and 10 and figures 1 and 2, the  $C_{max}$  for the CR tablets (treatments 1A, 1B, 2A and 2B) is considerably lower, and the  $T_{max}$  much higher  
15 than for the immediate release oxymorphone. The blood plasma level of oxymorphone remains high well past the 8 (or even the 12) hour dosing interval desired for an effective controlled release tablet.

Table 14 - Pharmacokinetic Parameters of Plasma Oxymorphone for Study 3

	Treatment 3A		Treatment 3B		Treatment 3C		Treatment 3D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C <sub>max</sub>	1.7895	0.6531	1.1410	0.4537	2.2635	1.0008	2.2635	1.0008
T <sub>max</sub>	5.65	9.39	5.57	7.14	0.978	1.14	0.978	1.14
AUC <sub>(0-t)</sub>	14.27	4.976	11.64	3.869	12.39	4.116	12.39	4.116
AUC <sub>(0-inf)</sub>	19.89	6.408	17.71	8.471	14.53	4.909	14.53	4.909
T <sub>1/2el</sub>	21.29	6.559	19.29	5.028	18.70	6.618	18.70	6.618
	12.0	3.64	12.3	3.99	16.2	11.4	16.2	11.4

The relative bioavailability calculations are summarized in tables 15 and 16.

Table 15 - Relative Bioavailability Determination Based on AUC<sub>(0-inf)</sub>

F <sub>rel</sub> (3A vs. 3C)	F <sub>rel</sub> (3B vs. 3D)	F <sub>rel</sub> (3D vs. 3C)	F <sub>rel</sub> (3A vs. 3B)
1.040 ± 0.1874	0.8863 ± 0.2569	1.368 ± 0.4328	1.169 ± 0.2041

5

Table 16 - Relative bioavailability Determination Based on AUC<sub>(0-24)</sub>

F <sub>rel</sub> (3A vs. 2C)	F <sub>rel</sub> (3B vs. 3D)	F <sub>rel</sub> (3D vs. 3C)	F <sub>rel</sub> (3A vs. 3B)
0.9598 ± 0.2151	0.8344 ± 0.100	1.470 ± 0.3922	1.299 ± 0.4638

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone controlled release (20 mg) compared to oxymorphone oral solution (10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of oxymorphone from the controlled release formulation,  
10 oxymorphone CR, and from the oral solution.

The presence of a high fat meal had a substantial effect on the oxymorphone C<sub>max</sub>, but less of an effect on oxymorphone AUC from oxymorphone controlled release tablets. Least Squares (LS) mean C<sub>max</sub> was 58% higher and LS mean AUC<sub>(0-t)</sub> and AUC<sub>(0-inf)</sub> were 18% higher for the fed condition (Treatment B) compared to the fasted condition  
15 (Treatment A) based on LN-transformed data. This was consistent with the relative

bioavailability determination from  $AUC_{(0-\infty)}$  since mean  $F_{rel}$  was 1.17. Mean  $T_{max}$  values were similar (approximately 5.6 hours), and no significant different in  $T_{max}$  was shown using nonparametric analysis. Half value durations were significantly different between the two treatments.

5       The effect of food on oxymorphone bioavailability from the oral solution was more pronounced, particularly in terms of AUC. LS mean  $C_{max}$  was 50% higher and LS mean  $AUC_{(0-t)}$  and  $AUC_{(0-\infty)}$  were 32-34% higher for the fed condition (Treatment D) compared to the fasted condition (Treatment C) based on LN-transformed data. This was consistent with the relative bioavailability determination from  $AUC_{(0-\infty)}$  since mean  $F_{rel}$   
10      was 1.37. Mean  $T_{max}$  (approximately 1 hour) was similar for the two treatments and no significant difference was shown.

15       Under fasted conditions, oxymorphone controlled release 20 mg tablets exhibited similar extent of oxymorphone availability compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean  $AUC_{(0-t)}$  was 17% higher for oxymorphone CR, whereas LS mean  $AUC_{(0-\infty)}$  values were nearly equal (mean ratio=99%). Mean  $F_{rel}$  values calculated from  $AUC_{(0-\infty)}$  and  $AUC_{(0-24)}$ , (1.0 and 0.96, respectively) also showed similar extent of oxymorphone availability between the two treatments.

20       As expected, there were differences in parameters reflecting rate of absorption. LS mean  $C_{max}$  was 49% lower for oxymorphone controlled release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Half-value duration was significantly longer for the controlled release formulation (means, 12 hours versus 2.5 hours).

25       Under fed conditions, oxymorphone availability from oxymorphone controlled release 20 mg was similar compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean  $AUC_{(0-\infty)}$  was 12% lower for oxymorphone CR. Mean  $F_{rel}$  values calculated from  $AUC_{(0-\infty)}$  and  $AUC_{(0-24)}$ , (0.89 and 0.83 respectively) also showed similar extent of oxymorphone availability from the tablet. As expected, there were differences in parameters reflecting rate of absorption. LS mean  $C_{max}$  was 46% lower for oxymorphone  
30

controlled release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Mean  $T_{max}$  was 5.7 hours for the tablet compared to 1.1 hours for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 7.8 hours versus 3.1 hours).

5       The presence of a high fat meal did not appear to substantially affect the availability following administration of oxymorphone controlled release tablets. LS mean ratios were 97% for  $AUC_{(0-t)}$  and 91% for  $C_{max}$  (Treatment B versus A), based on LN-transformed data. This was consistent with the relative bioavailability determination from  $AUC_{(0-24)}$ , since mean  $F_{rel}$  was 0.97. Mean  $T_{max}$  was later for the fed treatment  
10      compared to the fasted treatment (5.2 and 3.6 hours, respectively), and difference was significant.

Under fasted conditions, oxymorphone controlled release 20 mg tablets exhibited similar availability compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean ratio for  
15       $AUC_{(0-t)}$  was 104.5%. Mean  $F_{rel}$  (0.83) calculated from  $AUC_{(0-24)}$  also showed similar extent of oxymorphone availability between the two treatments. Mean  $T_{max}$  was 3.6 hours for the tablet compared to 0.88 for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 11 hours versus 2.2 hours).

20       Under fed conditions, availability from oxymorphone controlled release 20 mg was similar compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean  $AUC_{(0-t)}$  was 14% higher for oxymorphone CR. Mean  $F_{rel}$  (0.87) calculated from  $AUC_{(0-24)}$  also indicated similar extent of availability between the treatments. Mean  $T_{max}$  was 5.2 hours for the tablet compared to 1.3 hour for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 14 hours versus 3.9 hours).

30       The extent of oxymorphone availability from oxymorphone controlled release 20 mg tablets was similar under fed and fasted conditions since there was less than a 20% difference in LS mean  $AUC_{(0-t)}$  and  $AUC_{(0-\infty)}$  values for each treatment, based on LN-

transformed data.  $T_{max}$  was unaffected by food; however, LS mean  $C_{max}$  was increased 58% in the presence of the high fat meal. Both rate and extent of oxymorphone absorption from the oxymorphone oral solution were affected by food since LS mean  $C_{max}$  and AUC values were increased approximately 50 and 30%, respectively.  $T_{max}$  was 5 unaffected by food. Under both fed and fasted conditions, oxymorphone controlled release tablets exhibited similar extent of oxymorphone availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean AUC(0-t) and AUC(0-inf) values for each treatment.

Bioavailability following oxymorphone controlled release 20 mg tablets was also 10 similar under fed and fasted conditions since there was less than a 20% difference in LS mean  $C_{max}$  and AUC values for each treatment.  $T_{max}$  was later for the fed condition. The presence of food did not affect the extent of availability from oxymorphone oral solution since LS mean AUC values were less than 20% different. However,  $C_{max}$  was decreased 35% in the presence of food.  $T_{max}$  was unaffected by food. Under both fed 15 and fasted conditions, oxymorphone controlled release tablets exhibited similar extent of availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean AUC values for each treatment.

The mean 6-OH oxymorphone plasma concentration versus time curves for Treatments 3A, 3B, 3C, and 3D are presented in Figure 8. The data is contained in Table 20 17.

Table 17 - Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	6-Hydroxyoxymorphone			
	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
0	0.0069	0.0125	0.0741	0.0000
0.25			0.7258	0.4918
0.5	0.5080	0.1879	1.2933	0.5972
0.75			1.3217	0.7877
1	1.0233	0.4830	1.1072	0.8080
1.25			1.0069	0.7266
1.5	1.1062	0.7456	0.8494	0.7001
1.75			0.7511	0.6472
2	1.0351	0.7898	0.6554	0.5758
3	0.9143	0.7619	0.6196	0.5319
4	0.8522	0.7607	0.4822	0.5013
5	0.8848	0.8548	0.3875	0.4448
6	0.7101	0.7006	0.3160	0.3451
8	0.5421	0.5681	0.2525	0.2616
10	0.4770	0.5262	0.2361	0.2600
12	0.4509	0.4454	0.2329	0.2431
14	0.4190	0.4399	0.2411	0.2113
16	0.4321	0.4230	0.2385	0.2086
20	0.3956	0.4240	0.2234	0.1984
24	0.4526	0.4482	0.2210	0.2135
30	0.4499	0.4708		
36	0.3587	0.3697	0.1834	0.1672
48	0.3023	0.3279		

Table 18 - Pharmacokinetic Parameters of Plasma Oxymorphone for Study 3

	Treatment 3A		Treatment 3B		Treatment 3C		Treatment 3D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C <sub>max</sub>	1.2687	0.5792	1.1559	0.4848	1.5139	0.7616	0.9748	0.5160
T <sub>max</sub>	3.61	7.17	5.20	9.52	0.880	0.738	1.30	1.04
AUC <sub>(0-t)</sub>	22.47	10.16	22.01	10.77	10.52	4.117	9.550	4.281
AUC <sub>(0-inf)</sub>	38.39	23.02	42.37	31.57	20.50	7.988	23.84	11.37
T <sub>1/2el</sub>	39.1	36.9	39.8	32.6	29.3	12.0	44.0	35.00

**Study 4 - Controlled Release 20 mg vs Immediate Release 10 mg**

A study was conducted to compare the bioavailability and pharmacokinetics of controlled release and immediate release oxymorphone tablets under single-dose and multiple-dose (steady state) conditions. For the controlled release study, healthy  
5 volunteers received a single dose of a 20 mg controlled release oxymorphone tablet on the morning of Day 1. Beginning on the morning of Day 3, the volunteers were administered a 20 mg controlled release oxymorphone tablet every 12 hours through the morning dose of Day 9. For the immediate release study, healthy volunteers received a single 10 mg dose of an immediate release oxymorphone tablet on the morning of Day 1. On the  
10 morning of Day 3, additional 10 mg immediate release tablets were administered every six hours through the first two doses on Day 9.

Figure 9 shows the average plasma concentrations of oxymorphone and 6-6-hydroxy oxymorphone for all subjects after a single dose either controlled release (CR) 20 mg or immediate release (IR) 10 mg oxymorphone. The data in the figure (as with the  
15 other relative experimental data herein) is normalized to a 20 mg dose. The immediate release tablet shows a classical curve, with a high, relatively narrow peak followed by an exponential drop in plasma concentration. The controlled release oxymorphone tablets show a lower peak with extended moderate levels of oxymorphone and 6-hydroxy oxymorphone. Table 19 shows the levels of oxymorphone and 6-hydroxy oxymorphone  
20 from Figure 9 in tabular form.

Table 19 - Mean Plasma Concentration (ng/ml)

<u>Hour</u>	<u>Oxymorphone</u>		<u>6-Hydroxyoxymorphone</u>	
	<u>Controlled</u>	<u>Immediate</u>	<u>Controlled</u>	<u>Immediate</u>
	<u>Release</u>	<u>Release</u>	<u>Release</u>	<u>Release</u>
	<u>20 mg</u>	<u>10 mg</u>	<u>20 mg</u>	<u>10 mg</u>
0.00	0.00	0.00	0.00	0.00
0.25	0.22	1.08	0.14	0.73
0.50	0.59	1.69	0.45	1.22
1.00	0.77	1.19	0.53	0.79
1.50	0.84	0.91	0.53	0.57
2.00	0.87	0.75	0.60	0.47
3.00	0.83	0.52	0.55	0.34
4.00	0.73	0.37	0.53	0.27
5.00	0.94	0.36	0.46	0.23
6.00	0.81	0.28	0.41	0.18
8.00	0.73	0.20	0.37	0.14
10.0	0.60	0.19	0.35	0.15
12.0	0.67	0.25	0.32	0.13
16.0	0.39	0.16	0.29	0.13
24.0	0.23	0.07	0.29	0.13
30.0	0.12	0.01	0.17	0.04
36.0	0.05	0.00	0.11	0.00
48.0	0.00	0.00	0.07	0.01

Figure 10 shows the average plasma concentrations of oxymorphone and 6-hydroxyoxymorphone for all subjects in the steady state test, for doses of controlled release 20 mg tablets and immediate release 10 mg tablets of oxymorphone. The figure shows the plasma concentrations after the final controlled release tablet is given on Day 9, and the final immediate release tablet is given 12 hours thereafter. The steady state administration of the controlled release tablets clearly shows a steady moderate level of oxymorphone ranging from just over 1 ng/ml to almost 1.75 ng/ml over the course of a twelve hour period, where the immediate release tablet shows wide variations in blood

plasma concentration. Table 20 shows the levels of oxymorphone and 6-hydroxyoxymorphone from Figure 10 in tabular form.

Table 20 - Summary of Mean Plasma Concentration (ng/ml)

<u>Day</u>	<u>Hour</u>	<u>Oxymorphone</u>		<u>6-Hydroxyoxymorphone</u>	
		<u>Controlled</u>	<u>Immediate</u>	<u>Controlled</u>	<u>Immediate</u>
		<u>Release</u>	<u>Release</u>	<u>Release</u>	<u>Release</u>
		<u>20 mg</u>	<u>10 mg</u>	<u>20 mg</u>	<u>10 mg</u>
4	0.00	1.10	0.75	0.89	0.72
5	0.00	1.12	0.84	1.15	0.88
6	0.00	1.20	0.92	1.15	0.87
7	0.00	1.19	0.91	1.27	1.00
8	0.00	1.19	0.86	1.29	0.98
9	0.00	1.03	1.07	1.09	1.05
	0.25		2.64		1.70
	0.50		3.12	1.50	2.09
	1.00		2.47	1.70	1.68
	1.50		2.05	1.63	1.55
	2.00		1.78	1.64	1.30
	3.00		1.27	1.47	1.11
	4.00		0.98	1.39	0.98
	5.00		1.01	1.21	0.89
	6.00		0.90	1.06	0.84
	6.25		1.17		0.88
	6.50		1.88		1.06
	7.00		2.12		1.20
	7.50		2.24		1.15
	8.00	1.32	2.01	0.97	1.03
	9.00		1.52		0.90
	10.0	1.32	1.24	0.85	0.84
	11.0		1.11		0.74
	12.0	1.18	0.96	0.79	0.70

Table 21 - Mean Single-Dose Pharmacokinetic Results

	Controlled Release 20mg		Immediate Release 10 mg	
	oxymorphone	6-OH-oxymorphone	oxymorphone	6-OH-oxymorphone
AUC( <sub>0-t</sub> )	14.74	11.54	7.10	5.66
AUC ( <sub>0-inf</sub> )	15.33	16.40	7.73	8.45
C <sub>max</sub> (ng/ml)	1.12	0.68	1.98	1.40
T <sub>max</sub> (hr)	5.00	2.00	0.50	0.50
T <sub>½</sub> (hr)	9.25	26.09	10.29	29.48

Parent 6-OH oxymorphone AUC(<sub>0-t</sub>) values were lower than the parent compound after administration of either dosage form, but the AUC(<sub>0-inf</sub>) values are slightly higher  
5 due to the longer half-life for the metabolite. This relationship was similar for both the immediate-release (IR) and controlled release (CR) dosage forms. As represented by the average plasma concentration graph, the CR dosage form has a significantly longer time to peak oxymorphone concentration and a lower peak oxymorphone concentration. The 6-OH oxymorphone peak occurred sooner than the parent peak following the CR dosage  
10 form, and simultaneously with the parent peak following the IR dosage form.

It is important to note that while the present invention is described and exemplified using 20 mg tablets, the invention may also be used with other strengths of tablets. In each strength, it is important to note how a 20 mg tablet of the same composition (except for the change in strength) would act. The blood plasma levels and  
15 pain intensity information are provided for 20 mg tablets, however the present invention is also intended to encompass 5 to 80 mg controlled release tablets. For this reason, the blood plasma level of oxymorphone or 6-hydroxyoxymorphone in nanograms per milliliter of blood, per mg oxymorphone (ng/mg·ml) administered is measured. Thus at 0.02 ng/mg·ml, a 5 mg tablet should produce a minimum blood plasma concentration of  
20 0.1 ng/ml. A stronger tablet will produce a higher blood plasma concentration of active molecule, generally proportionally. Upon administration of a higher dose tablet, for example 80 mg, the blood plasma level of oxymorphone and 6-OH oxymorphone may more than quadruple compared to a 20 mg dose, although conventional treatment of low

bioavailability substances would lead away from this conclusion. If this is the case, it may be because the body can only process a limited amount oxymorphone at one time. Once the bolus is processed, the blood level of oxymorphone returns to a proportional level.

5 It is the knowledge that controlled release oxymorphone tablets are possible to produce and effective to use, which is most important, made possible with the high bioavailability of oxymorphone in a controlled release tablet. This also holds true for continuous periodic administration of controlled release formulations. The intent of a controlled release opioid formulation is the long-term management of pain. Therefore,  
10 the performance of a composition when administered periodically (one to three times per day) over several days is important. In such a regime, the patient reaches a "steady state" where continued administration will produce the same results, when measured by duration of pain relief and blood plasma levels of pharmaceutical. Such a test is referred to as a "steady state" test and may require periodic administration over an extended time  
15 period ranging from several days to a week or more. Of course, since a patient reaches steady state in such a test, continuing the test for a longer time period should not affect the results. Further, when testing blood plasma levels in such a test, if the time period for testing exceeds the interval between doses, it is important the regimen be stopped after the test is begun so that observations of change in blood level and pain relief may be  
20 made without a further dose affecting these parameters.

**Study 5 - Controlled Release 40 mg vs Immediate Release 4 x 10 mg under Fed and Fasting Conditions**

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone controlled release (40 mg) compared to oxymorphone  
25 immediate release (4 x 10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of oxymorphone from the controlled release formulation, oxymorphone CR, and from the immediate release formulation, oxymorphone IR.

This study had a single-center, open-label, analytically blinded, randomized, four-way crossover design. Subjects randomized to Treatment 5A and Treatment 5C, as  
30 described below, were in a fasted state following a 10-hour overnight fast. Subjects

randomized to Treatment 5B and Treatment 5D, as described below, were in the fed state, having had a high fat meal, completed ten minutes prior to dosing. There was a 14-day washout interval between the four dose administrations. The subjects were confined to the clinic during each study period. Subject assigned to receive Treatment 5A and 5 Treatment 5B were discharged from the clinic on Day 3 following the 48-hour procedures, and subjects assigned to receive Treatment 5C and Treatment 5D were discharged from the clinic on Day 2 following the 36-hour procedures. On Day 1 of each study period the subjects received one of four treatments:

- 10        Treatments 5A and 5B: Oxymorphone controlled release 40 mg tablets from Table 2. Subjects randomized to Treatment 5A received a single oral dose of one 40 mg oxymorphone controlled release tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 5B received a single oral dose of one 40 mg oxymorphone controlled release tablet taken with 240 ml of water 10 minutes after a standardized high fat meal.
- 15        Treatments 5C and 5D: Immediate release tablet (IR) 4 x 10 mg Oxymorphone. Subjects randomized to Treatment 5C received a single oral dose of 4 x 10 mg oxymorphone IR tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 5D received a single oral dose of 4 x 10 mg oxymorphone IR tablet taken with 240 ml of water 10 minutes after a standardized high-fat meal.

A total of 28 male subjects were enrolled in the study, and 25 subjects completed the study. A total of 28 subjects received at least one treatment. Only subjects who completed all 4 treatments were included in the summary statistics and statistical analysis.

25        Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 60, and 72 hours post-dose (19 samples) for subjects randomized to all Treatments.

The mean oxymorphone plasma concentration versus time curves for Treatments 5A, 5B, 5C, and 5D are presented in Figure 11. The data is contained in Table 22. The

arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistics for all Treatments are summarized in Table 23.

Table 22 - Mean Plasma Concentration vs. Time (ng/ml)

<u>Time (hr)</u>	<u>Treatment 5A</u>	<u>Treatment 5B</u>	<u>Treatment 5C</u>	<u>Treatment 5D</u>
0	0.00	0.00	0.00	0.00
0.25	0.47	0.22	3.34	1.79
0.50	1.68	0.97	7.28	6.59
0.75	1.92	1.90	6.60	9.49
1	2.09	2.61	6.03	9.91
1.5	2.18	3.48	4.67	8.76
2	2.18	3.65	3.68	7.29
3	2.00	2.86	2.34	4.93
4	1.78	2.45	1.65	3.11
5	1.86	2.37	1.48	2.19
6	1.67	2.02	1.28	1.71
8	1.25	1.46	0.92	1.28
10	1.11	1.17	0.78	1.09
12	1.34	1.21	1.04	1.24
24	0.55	0.47	0.40	0.44
36	0.21	0.20	0.16	0.18
48	0.06	0.05	0.04	0.05
60	0.03	0.01	0.01	0.01
72	0.00	0.00	0.00	0.00

5

Table 23 - Pharmacokinetic Parameters of Plasma Oxymorphone for Study 5

	<u>Treatment 5A</u>		<u>Treatment 5B</u>		<u>Treatment 5C</u>		<u>Treatment 5D</u>	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
$C_{max}$	2.79	0.84	4.25	1.21	9.07	4.09	12.09	5.42
$T_{max}$	2.26	2.52	1.96	1.06	0.69	0.43	1.19	0.62
$AUC_{(0-t)}$	35.70	10.58	38.20	11.04	36.00	12.52	51.35	20.20
$AUC_{(0-\infty)}$	40.62	11.38	41.17	10.46	39.04	12.44	54.10	20.26
$T_{1/2el}$	12.17	7.57	10.46	5.45	11.65	6.18	9.58	3.63

The relative bioavailability calculations are summarized in Tables 24 and 25.

Table 24 - Relative Bioavailability Determination Based on AUC<sub>(0-inf)</sub>

F <sub>rel</sub> (5D vs. 5C)	F <sub>rel</sub> (5B vs. 5A)
1.3775	1.0220

Table 25 - Relative bioavailability Determination Based on AUC<sub>(0-24)</sub>

F <sub>rel</sub> (5D vs. 5C)	F <sub>rel</sub> (5B vs. 5A)
1.4681	1.0989

The mean 6-OH oxymorphone plasma concentration versus time curves for Treatments 5A, 5B, 5C, and 5D are presented in Figure 12. The data is contained in  
5 Table 26.

Table 26 - Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	6-Hydroxyoxymorphone			
	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
0	0.00	0.00	0.00	0.00
0.25	0.27	0.05	2.36	0.50
0.50	1.32	0.31	5.35	1.98
0.75	1.37	0.59	4.53	2.97
1	1.44	0.82	3.81	2.87
1.5	1.46	1.09	2.93	2.58
2	1.46	1.28	2.37	2.29
3	1.39	1.14	1.69	1.72
4	1.25	1.14	1.33	1.26
5	1.02	1.00	1.14	1.01
6	0.93	0.86	0.94	0.86
8	0.69	0.72	0.73	0.77
10	0.68	0.67	0.66	0.75
12	0.74	0.66	0.70	0.77
24	0.55	0.52	0.54	0.61
36	0.23	0.30	0.28	0.27
48	0.18	0.20	0.20	0.19
60	0.09	0.10	0.09	0.09
72	0.06	0.06	0.04	0.05

Table 27 - Pharmacokinetic Parameters of Plasma 6-Hydroxyoxymorphone for Study 5

	Treatment 5A		Treatment 5B		Treatment 5C		Treatment 5D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C <sub>max</sub>	1.88	0.69	1.59	0.63	6.41	3.61	3.79	1.49
T <sub>max</sub>	1.48	1.18	2.73	1.27	0.73	0.47	1.18	0.74
AUC <sub>(0-t)</sub>	28.22	10.81	26.95	11.39	33.75	10.29	32.63	13.32
AUC <sub>(0-inf)</sub>	33.15	11.25	32.98	10.68	37.63	17.01	36.54	13.79
T <sub>1/2el</sub>	17.08	7.45	21.92	8.41	16.01	6.68	16.21	7.42

The above description incorporates preferred embodiments and examples as a means of describing and enabling the invention to be practiced by one of skill in the art. It is imagined that changes can be made without departing from the spirit and scope of  
5 the invention described herein and defined in the appended claims.

## Claims:

1. A controlled release oxymorphone formulation comprising a controlled release matrix and from about 5 mg to about 80 mg oxymorphone wherein said formulation provides a maximum blood concentration of oxymorphone of between about 0.1 ng/ml and about 7.5 ng/ml upon oral administration of a single dose to a subject.
- 5
2. The controlled release oxymorphone formulation of claim 1 wherein said formulation comprises from about 5 mg to about 10 mg oxymorphone and said formulation provides a maximum blood concentration of oxymorphone of between about 0.12 ng/ml and about 1.0 ng/ml upon oral administration of a single dose to a subject.
- 10
3. The controlled release oxymorphone formulation of claim 1 wherein said formulation comprises from about 10 mg to about 20 mg oxymorphone and said formulation provides a maximum blood concentration of oxymorphone of between about 0.3 ng/ml and about 1.6 ng/ml upon oral administration of a single dose to a subject
- 15
4. The controlled release oxymorphone formulation of claim 1 wherein said formulation comprises from about 20 mg to about 40 mg oxymorphone and said formulation provides a maximum blood concentration of oxymorphone of between about 0.5 ng/ml and about 3.5 ng/ml upon oral administration of a single dose to a subject.
- 20
5. The controlled release oxymorphone formulation of claim 1 wherein said formulation comprises from about 40 mg to about 80 mg oxymorphone and said formulation provides a maximum blood concentration of oxymorphone of between about 1.5 ng/ml and about 7.5 ng/ml upon oral administration of a single dose to a subject.
- 6.
6. The controlled release oxymorphone formulation of claim 2 wherein said formulation provides a maximum blood concentration of oxymorphone of between about 0.17 ng/ml and about 0.75 ng/ml upon oral administration of a single dose to a subject.
- 25
7. The controlled release oxymorphone formulation of claim 3 wherein said formulation provides a maximum blood concentration of oxymorphone of between about 0.4 ng/ml and about 1.4 ng/ml upon oral administration of a single dose to a subject.

8. The controlled release oxymorphone formulation of claim 4 wherein said formulation provides a maximum blood concentration of oxymorphone of between about 0.9 ng/ml and about 3.0 ng/ml upon oral administration of a single dose to a subject.
9. The controlled release oxymorphone formulation of claim 5 wherein said formulation provides a maximum blood concentration of oxymorphone of between about 1.9 ng/ml and about 6.0 ng/ml upon oral administration of a single dose to a subject.
10. A controlled release oxymorphone formulation according to claim 2 wherein said formulation contains about 5 mg oxymorphone and wherein said formulation provides a maximum blood concentration of oxymorphone of between about 0.12 ng/ml and about 0.4 ng/ml upon oral administration of a single dose to a subject.
11. A controlled release oxymorphone formulation according to claim 3 wherein said formulation contains about 10 mg oxymorphone and wherein said formulation provides a maximum blood concentration of oxymorphone of between about 0.3 ng/ml and about 0.9 ng/ml upon oral administration of a single dose to a subject.
12. A controlled release oxymorphone formulation according to claim 4 wherein said formulation contains about 20 mg oxymorphone and wherein said formulation provides a maximum blood concentration of oxymorphone of between about 0.5 ng/ml and about 1.6 ng/ml upon oral administration of a single dose to a subject.
13. A controlled release oxymorphone formulation according to claim 5 wherein said formulation contains about 40 mg oxymorphone and wherein said formulation provides a maximum blood concentration of oxymorphone of between about 1.5 ng/ml and about 3.5 ng/ml upon oral administration of a single dose to a subject.
14. A controlled release oxymorphone formulation according to claim 5 wherein said formulation contains about 80 mg oxymorphone and wherein said formulation provides a maximum blood concentration of oxymorphone of between about 3.5 ng/ml and about 7.5 ng/ml upon oral administration of a single dose to a subject.
15. A controlled release oxymorphone formulation according to claim 10 wherein said formulation provides a maximum blood concentration of oxymorphone of between about 0.15 ng/ml and about 0.35 ng/ml upon oral administration of a single dose to a subject.

16. A controlled release oxymorphone formulation according to claim 11 wherein said formulation provides a maximum blood concentration of oxymorphone of between about 0.5 ng/ml and about 0.75 ng/ml upon oral administration of a single dose to a subject.
17. A controlled release oxymorphone formulation according to claim 12 wherein said 5 formulation provides a maximum blood concentration of oxymorphone of between about 0.75 ng/ml and about 1.4 ng/ml upon oral administration of a single dose to a subject.
18. A controlled release oxymorphone formulation according to claim 13 wherein said formulation provides a maximum blood concentration of oxymorphone of between about 2.0 ng/ml and about 3.0 ng/ml upon oral administration of a single dose to a subject.
- 10 19. A controlled release oxymorphone formulation according to claim 14 wherein said formulation provides a maximum blood concentration of oxymorphone of between about 4.0 ng/ml and about 6.5 ng/ml upon oral administration of a single dose to a subject.
20. A controlled release oxymorphone formulation comprising a controlled release matrix and from about 5 mg to about 80 mg oxymorphone wherein said formulation 15 provides a maximum blood concentration of 6-OH oxymorphone of between about 0.05 ng/ml and about 5.0 ng/ml upon oral administration of a single dose to a subject.
21. The controlled release oxymorphone formulation of claim 20 wherein said formulation comprises from about 5 mg to about 10 mg oxymorphone and said formulation provides a maximum blood concentration of 6-OH oxymorphone of between 20 about 0.05 ng/ml and about 0.6 ng/ml upon oral administration of a single dose to a subject.
22. The controlled release oxymorphone formulation of claim 20 wherein said formulation comprises from about 10 mg to about 20 mg oxymorphone and said formulation provides a maximum blood concentration of 6-OH oxymorphone of between 25 about 0.1 ng/ml and about 1.25 ng/ml upon oral administration of a single dose to a subject.
23. The controlled release oxymorphone formulation of claim 20 wherein said formulation comprises from about 20 mg to about 40 mg oxymorphone and said formulation provides a maximum blood concentration of 6-OH oxymorphone of between

- about 0.2 ng/ml and about 2.5 ng/ml upon oral administration of a single dose to a subject.
24. The controlled release oxymorphone formulation of claim 20 wherein said formulation comprises from about 40 mg to about 80 mg oxymorphone and said formulation provides a maximum blood concentration of 6-OH oxymorphone of between about 0.4 ng/ml and about 5.0 ng/ml upon oral administration of a single dose to a subject.  
5
25. The controlled release oxymorphone formulation of claim 21 wherein said formulation provides a maximum blood concentration of 6-OH oxymorphone of between about 0.1 ng/ml and about 0.4 ng/ml upon oral administration of a single dose to a subject.  
10
26. The controlled release oxymorphone formulation of claim 22 wherein said formulation provides a maximum blood concentration of 6-OH oxymorphone of between about 0.2 ng/ml and about 0.8 ng/ml upon oral administration of a single dose to a subject.  
15
27. The controlled release oxymorphone formulation of claim 23 wherein said formulation provides a maximum blood concentration of 6-OH oxymorphone of between about 0.4 ng/ml and about 1.6 ng/ml upon oral administration of a single dose to a subject.
- 20 28. The controlled release oxymorphone formulation of claim 24 wherein and said formulation provides a maximum blood concentration of 6-OH oxymorphone of between about 0.8 ng/ml and about 3.2 ng/ml upon oral administration of a single dose to a subject.
29. A controlled release oxymorphone formulation according to claim 21 wherein said formulation contains about 5 mg oxymorphone and wherein said formulation provides a maximum blood concentration of 6-OH oxymorphone of between about 0.05 ng/ml and about 0.3 ng/ml upon oral administration of a single dose to a subject.  
25
30. A controlled release oxymorphone formulation according to claim 21 wherein said formulation contains about 10 mg oxymorphone and wherein said formulation provides a

maximum blood concentration of 6-OH oxymorphone of between about 0.1 ng/ml and about 0.6 ng/ml upon oral administration of a single dose to a subject.

31. A controlled release oxymorphone formulation according to claim 22 wherein said formulation contains about 20 mg oxymorphone and wherein said formulation provides a maximum blood concentration of 6-OH oxymorphone of between about 0.2 ng/ml and about 1.2 ng/ml upon oral administration of a single dose to a subject.

5 32. A controlled release oxymorphone formulation according to claim 23 wherein said formulation contains about 40 mg oxymorphone and wherein said formulation provides a maximum blood concentration of 6-OH oxymorphone of between about 0.4 ng/ml and 10 about 2.4 ng/ml upon oral administration of a single dose to a subject.

33. A controlled release oxymorphone formulation according to claim 24 wherein said formulation contains about 80 mg oxymorphone and wherein said formulation provides a maximum blood concentration of 6-OH oxymorphone of between about 0.8 ng/ml and about 4.8 ng/ml upon oral administration of a single dose to a subject.

15 34. A controlled release oxymorphone formulation according to claim 29 wherein said formulation provides a maximum blood concentration of 6-OH oxymorphone of between about 0.1 ng/ml and about 0.25 ng/ml upon oral administration of a single dose to a subject.

20 35. A controlled release oxymorphone formulation according to claim 30 wherein said formulation provides a maximum blood concentration of 6-OH oxymorphone of between about 0.2 ng/ml and about 0.5 ng/ml upon oral administration of a single dose to a subject.

25 36. A controlled release oxymorphone formulation according to claim 31 wherein formulation provides a maximum blood concentration of 6-OH oxymorphone of between about 0.4 ng/ml and about 1.0 ng/ml upon oral administration of a single dose to a subject.

37. A controlled release oxymorphone formulation according to claim 32 wherein said formulation provides a maximum blood concentration of 6-OH oxymorphone of between

about 0.8 ng/ml and about 2.0 ng/ml upon oral administration of a single dose to a subject.

38. A controlled release oxymorphone formulation according to claim 33 wherein said formulation provides a maximum blood concentration of 6-OH oxymorphone of between  
5 about 1.6 ng/ml and about 4.0 ng/ml upon oral administration of a single dose to a subject.

39. A controlled release oxymorphone formulation comprising a controlled release matrix and from about 5 mg to about 80 mg oxymorphone wherein said formulation provides a minimum blood concentration of oxymorphone of at least about 0.02  
10 ng/mg·ml at about 12 hours after oral administration of a single dose to a subject.

40. The controlled release oxymorphone formulation of claim 39 wherein said formulation contains about 5 mg oxymorphone.

41. The controlled release oxymorphone formulation of claim 39 wherein said formulation contains about 10 mg oxymorphone.

15 42. The controlled release oxymorphone formulation of claim 39 wherein said formulation contains about 20 mg oxymorphone.

43. The controlled release oxymorphone formulation of claim 39 wherein said formulation contains about 40 mg oxymorphone.

44. The controlled release oxymorphone formulation of claim 39 wherein said  
20 formulation contains about 80 mg oxymorphone.

45. The controlled release oxymorphone formulation of claim 40 wherein said formulation provides a minimum blood concentration of oxymorphone of at least about 0.13 ng/ml at about 12 hours after oral administration of a single dose to a subject.

46. The controlled release oxymorphone formulation of claim 41 wherein said  
25 formulation provides a minimum blood concentration of oxymorphone of at least about 0.25 ng/ml at about 12 hours after oral administration of a single dose to a subject.

47. The controlled release oxymorphone formulation of claim 42 wherein said formulation provides a minimum blood concentration of oxymorphone of at least about 0.5 ng/ml at about 12 hours after oral administration of a single dose to a subject.
48. The controlled release oxymorphone formulation of claim 43 wherein said 5 formulation provides a minimum blood concentration of oxymorphone of at least about 1.0 ng/ml at about 12 hours after oral administration of a single dose to a subject.
49. The controlled release oxymorphone formulation of claim 44 wherein said formulation provides a minimum blood concentration of oxymorphone of at least about 2.0 ng/ml at about 12 hours after oral administration of a single dose to a subject.
- 10 50. A controlled release oxymorphone formulation comprising a controlled release matrix and from about 5 mg to about 80 mg oxymorphone wherein said formulation provides a minimum blood concentration of 6-OH oxymorphone of at least about 0.010 ng/mg·ml at about 12 hours after oral administration of a single dose to a subject.
51. The controlled release oxymorphone formulation of claim 50 wherein said 15 formulation contains about 5 mg oxymorphone.
52. The controlled release oxymorphone formulation of claim 50 wherein said formulation contains about 10 mg oxymorphone.
53. The controlled release oxymorphone formulation of claim 50 wherein said formulation contains about 20 mg oxymorphone.
- 20 54. The controlled release oxymorphone formulation of claim 50 wherein said formulation contains about 40 mg oxymorphone.
55. The controlled release oxymorphone formulation of claim 50 wherein said formulation contains about 80 mg oxymorphone.
56. The controlled release oxymorphone formulation of claim 51 wherein said 25 formulation provides a minimum blood concentration of 6-OH oxymorphone of at least about 0.065 ng/ml at about 12 hours after oral administration of a single dose to a subject.

57. The controlled release oxymorphone formulation of claim 52 wherein said formulation provides a minimum blood concentration of 6-OH oxymorphone of at least about 0.13 ng/ml at about 12 hours after oral administration of a single dose to a subject.

58. The controlled release oxymorphone formulation of claim 53 wherein said formulation provides a minimum blood concentration of 6-OH oxymorphone of at least about 0.25 ng/ml at about 12 hours after oral administration of a single dose to a subject.

59. The controlled release oxymorphone formulation of claim 54 wherein said formulation provides a minimum blood concentration of 6-OH oxymorphone of at least about 0.5 ng/ml at about 12 hours after oral administration of a single dose to a subject.

10 60. The controlled release oxymorphone formulation of claim 55 wherein said formulation provides a minimum blood concentration of 6-OH oxymorphone of at least about 1.0 ng/ml at about 12 hours after oral administration of a single dose to a subject.

15 61. A controlled release oxymorphone formulation comprising a controlled release matrix and from about 5 mg to about 80 mg oxymorphone wherein upon repeated oral administration of said formulation to a subject every 8 to 12 hours through steady state conditions, said formulation provides a minimum blood concentration of oxymorphone of at least about 0.025 ng/mg·ml at about 12 hours after administration.

62. The controlled release oxymorphone formulation of claim 61 wherein said formulation contains about 5 mg oxymorphone.

20 63. The controlled release oxymorphone formulation of claim 61 wherein said formulation contains about 10 mg oxymorphone.

64. The controlled release oxymorphone formulation of claim 61 wherein said formulation contains about 20 mg oxymorphone.

25 65. The controlled release oxymorphone formulation of claim 61 wherein said formulation contains about 40 mg oxymorphone.

66. The controlled release oxymorphone formulation of claim 61 wherein said formulation contains about 80 mg oxymorphone.

67. A controlled release oxymorphone formulation comprising a controlled release matrix and from about 5 mg to about 80 mg oxymorphone wherein upon repeated oral administration of said formulation to a subject every 8 to 12 hours through steady state conditions, said formulation provides a minimum blood concentration of 6-OH oxymorphone of at least about 0.03 ng/mg·ml at about 12 hours after administration.

5 68. The controlled release oxymorphone formulation of claim 67 wherein said formulation contains about 5 mg oxymorphone.

69. The controlled release oxymorphone formulation of claim 67 wherein said formulation contains about 10 mg oxymorphone.

10 70. The controlled release oxymorphone formulation of claim 67 wherein said formulation contains about 20 mg oxymorphone.

71. The controlled release oxymorphone formulation of claim 67 wherein said formulation contains about 40 mg oxymorphone.

15 72. The controlled release oxymorphone formulation of claim 67 wherein said formulation contains about 80 mg oxymorphone.

73. A method of controlling pain in a patient for 8 hours comprising administering to said patient a single dose of a pharmaceutical preparation comprising from about 5 mg to about 80 mg oxymorphone which induces in the patient a blood plasma concentration of oxymorphone of at least 0.02 ng/mg·ml at least 12 hours after said administration.

20 74. The method of claim 73 wherein said pharmaceutical preparation contains 5 mg oxymorphone.

75. The method of claim 73 wherein said pharmaceutical preparation contains 10 mg oxymorphone.

25 76. The method of claim 73 wherein said pharmaceutical preparation contains 20 mg oxymorphone.

77. The method of claim 73 wherein said pharmaceutical preparation contains 40 mg oxymorphone.

78. The method of claim 73 wherein said pharmaceutical preparation contains 80 mg oxymorphone.

79. A method of controlling pain in a patient for 8 hours comprising administering to said patient a single dose of a pharmaceutical preparation comprising from about 5 mg to 5 about 80 mg oxymorphone which induces in the patient a blood plasma concentration of 6-OH oxymorphone of at least 0.014 ng/mg·ml at least 12 hours after said administration.

80. The method of claim 79 wherein said pharmaceutical preparation contains 5 mg oxymorphone.

81. The method of claim 79 wherein said pharmaceutical preparation contains 10 mg 10 oxymorphone.

82. The method of claim 79 wherein said pharmaceutical preparation contains 20 mg oxymorphone.

83. The method of claim 79 wherein said pharmaceutical preparation contains 40 mg oxymorphone.

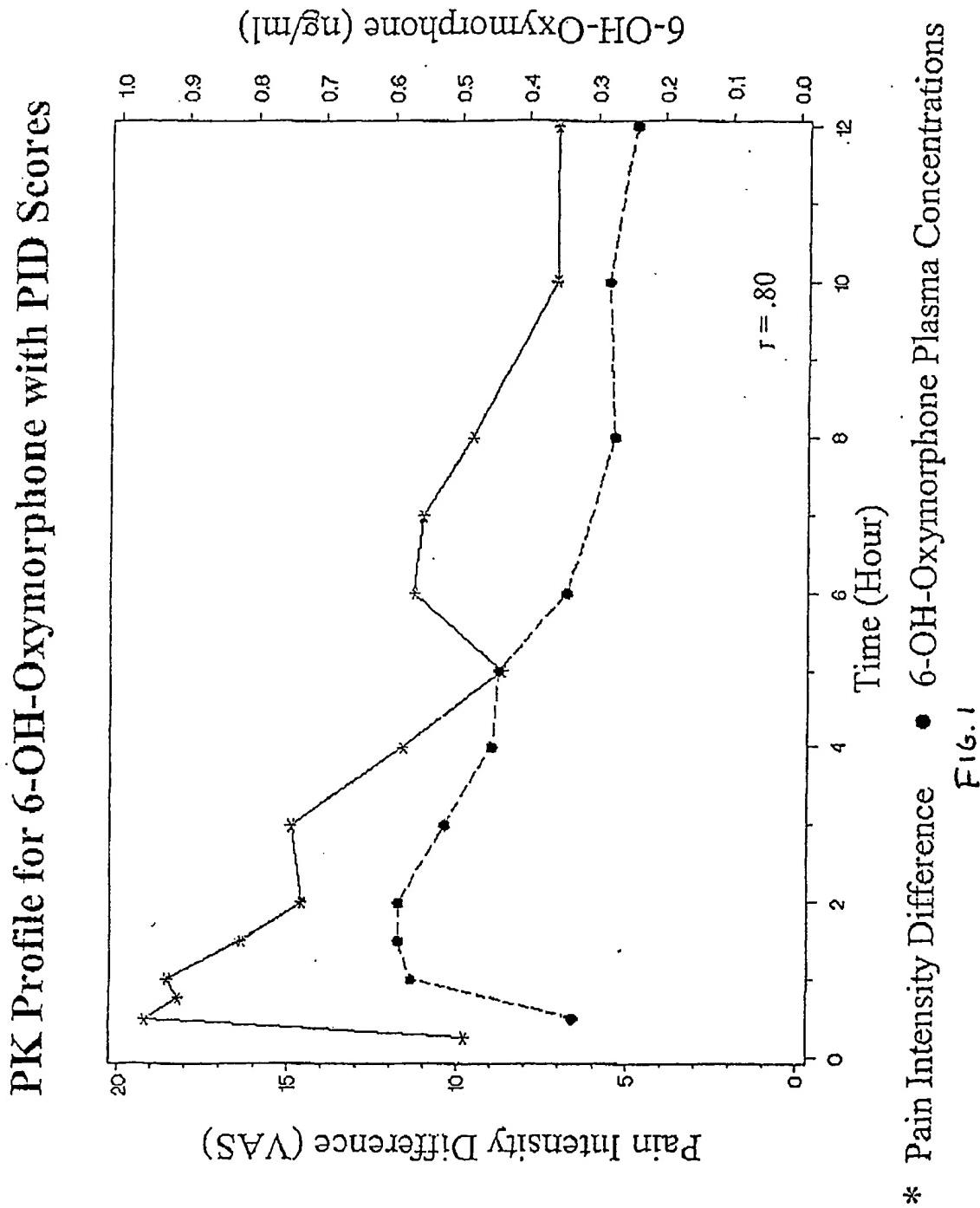
15 84. The method of claim 79 wherein said pharmaceutical preparation contains 80 mg oxymorphone.

85. A controlled release pharmaceutical formulation comprising a controlled release matrix and about 5 to about 80 mg oxymorphone wherein the relative bioavailability of oxymorphone to an equal dose of an immediate release formulation of oxymorphone is 20 from about 0.5 to about 1.5 upon oral administration of a single dose to a subject.

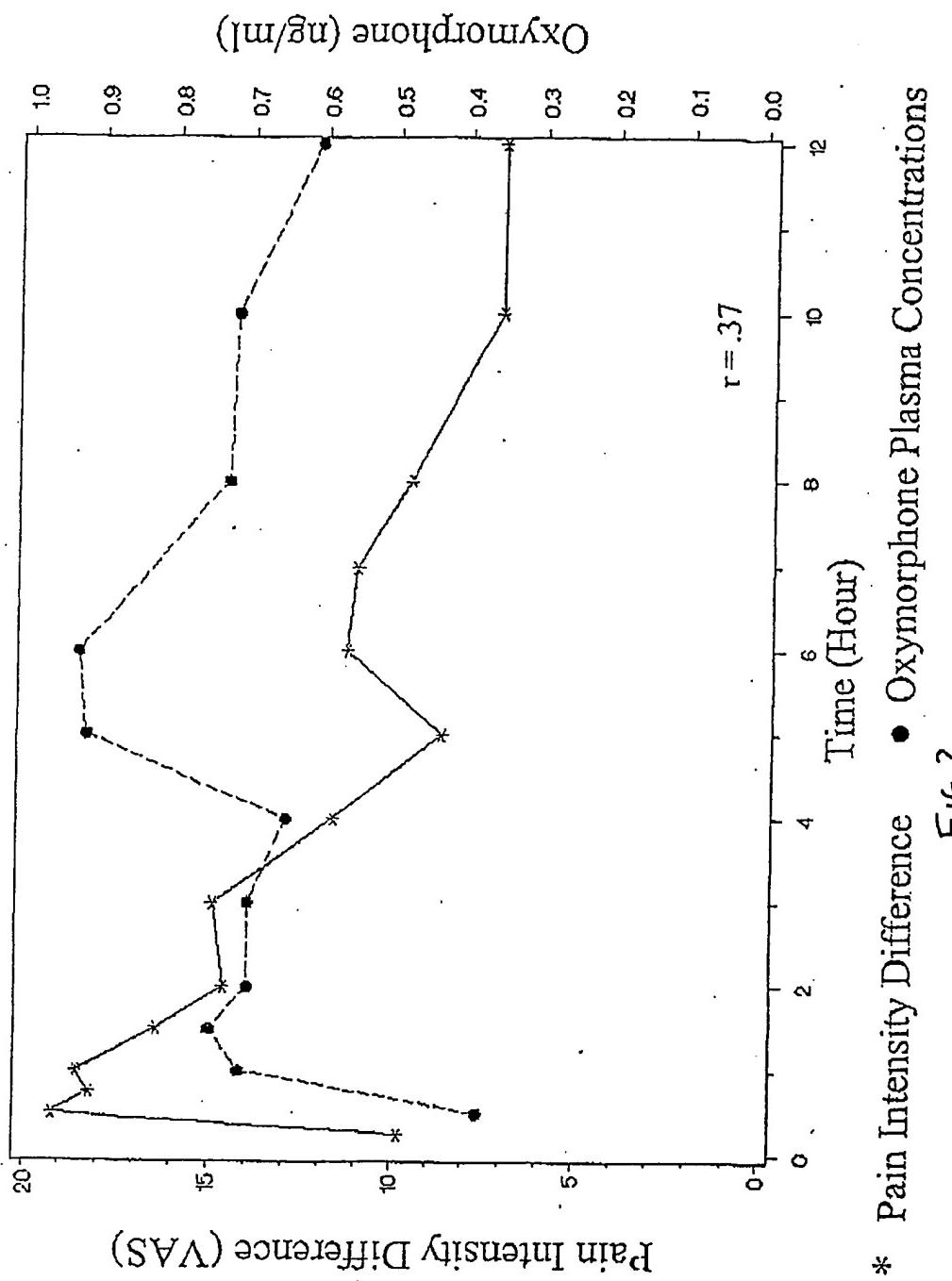
86. A controlled release pharmaceutical formulation comprising a controlled release matrix and about 5 to about 80 mg oxymorphone wherein the ratio of the area under the blood plasma concentration versus time curve of 6-OH-oxymorphone to oxymorphone, from time 0 to infinity ( $AUC_{(0-\infty)}$ ) is in the range of about 0.5 to about 1.5 upon oral 25 administration of a single dose of the formulation to a subject.

87. A controlled release pharmaceutical formulation comprising a controlled release matrix and about 5 to about 80 mg oxymorphone wherein upon repeated oral

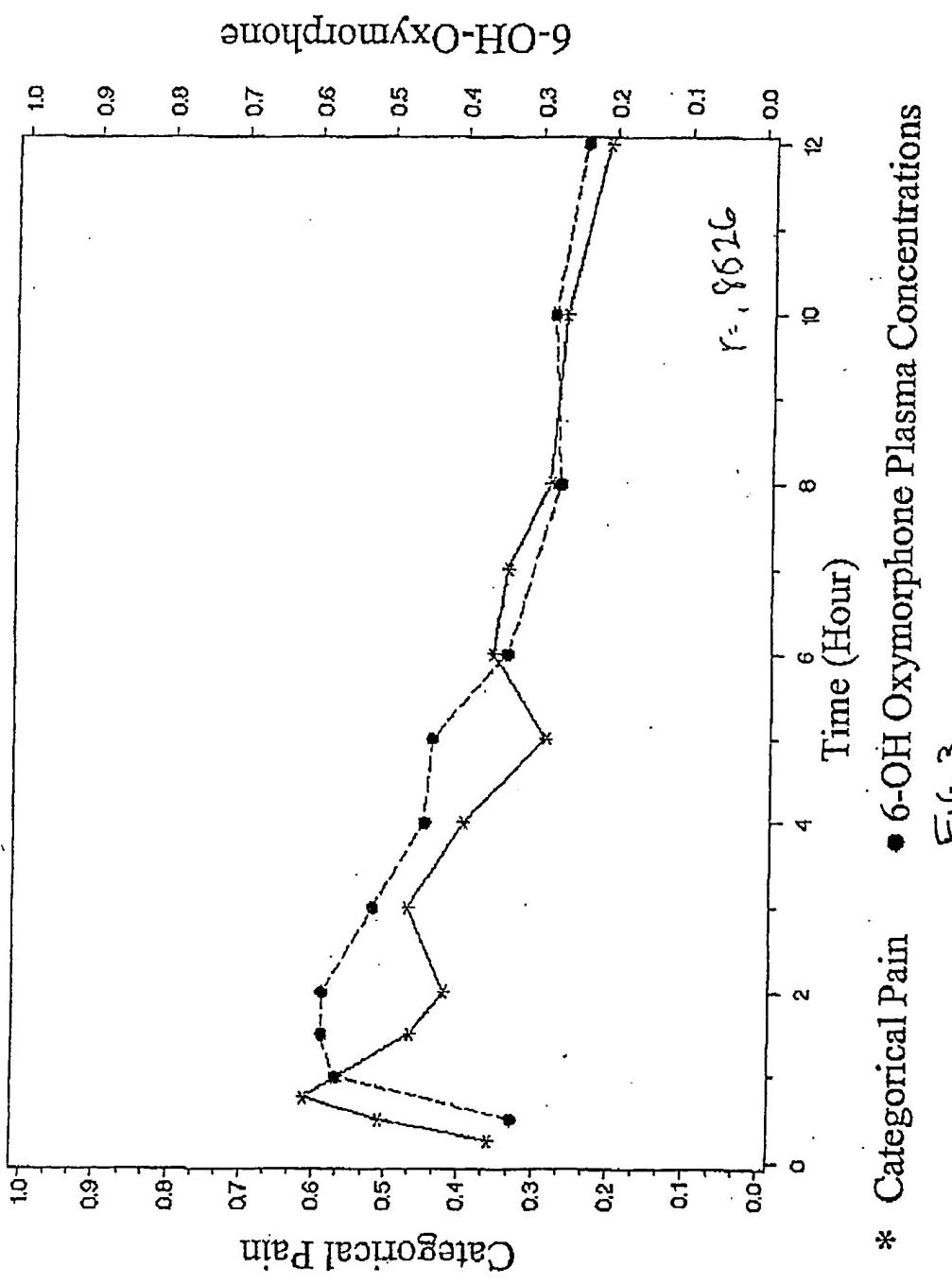
administration of said formulation to a subject every 8 to 12 hours through steady state conditions, the ratio of the area under the blood plasma concentration versus time curve of 6-OH-oxymorphone to oxymorphone, from time 0 to infinity ( $AUC_{(0-\infty)}$ ) is in the range of about 0.5 to about 1.5 upon oral administration a last dose of the formulation to  
5 a subject.



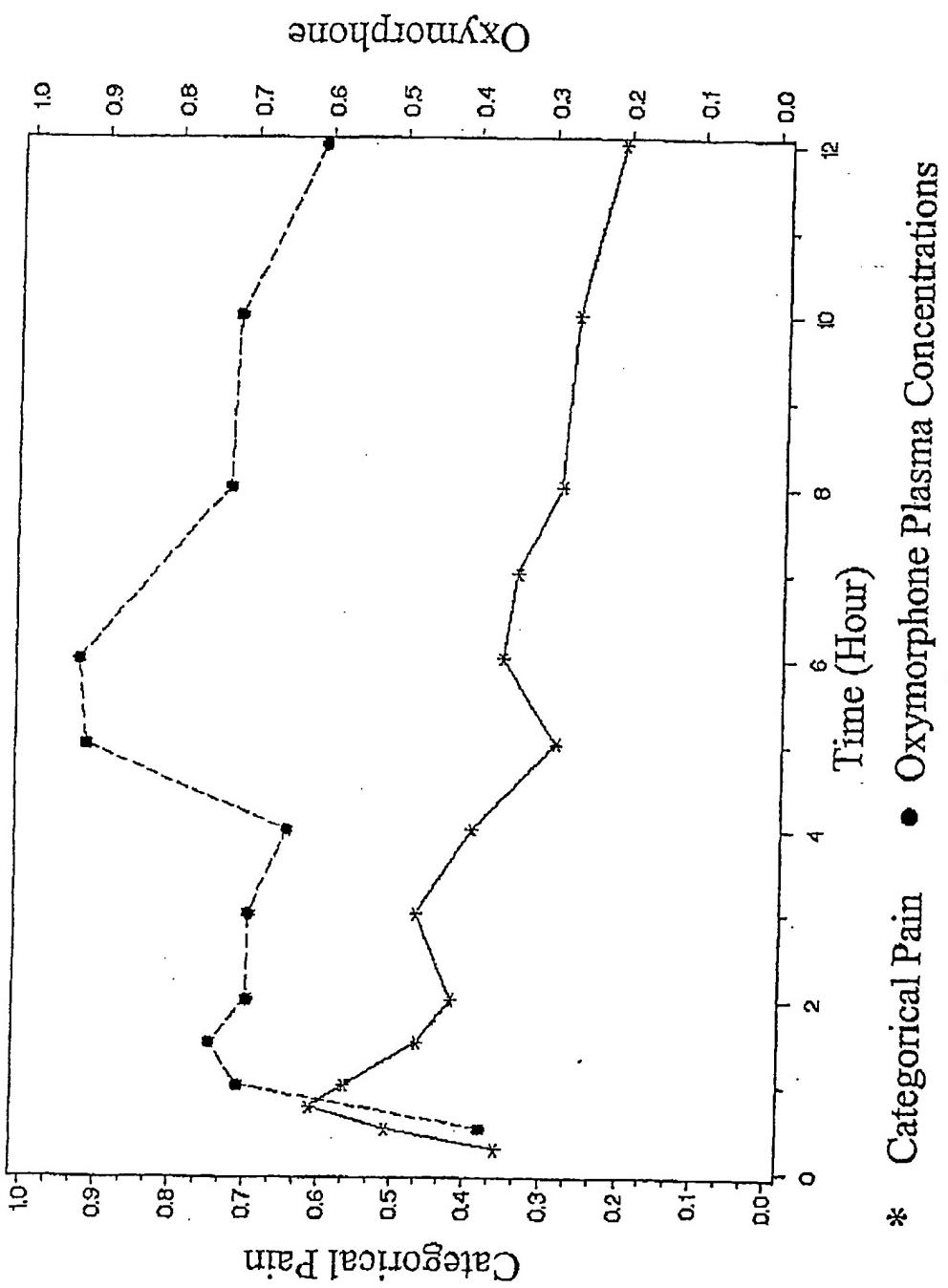
PK Profile for Oxymorphone with PID Scores



### PK Profile for 6-OH-Oxymorphone with Categorical Pain Scores



### PK Profile for Oxymorphone with Categorical Pain Scores



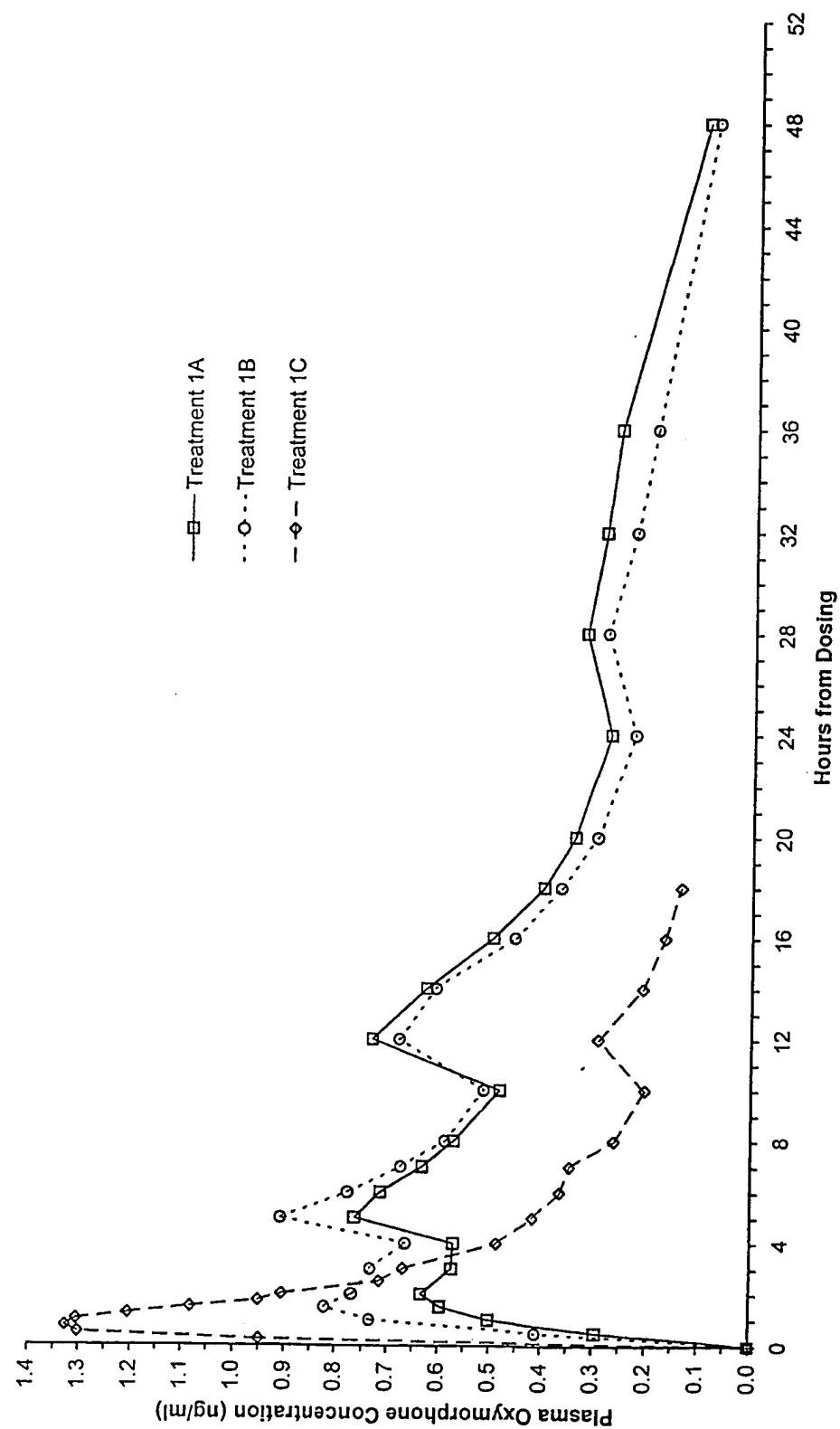


Figure 5

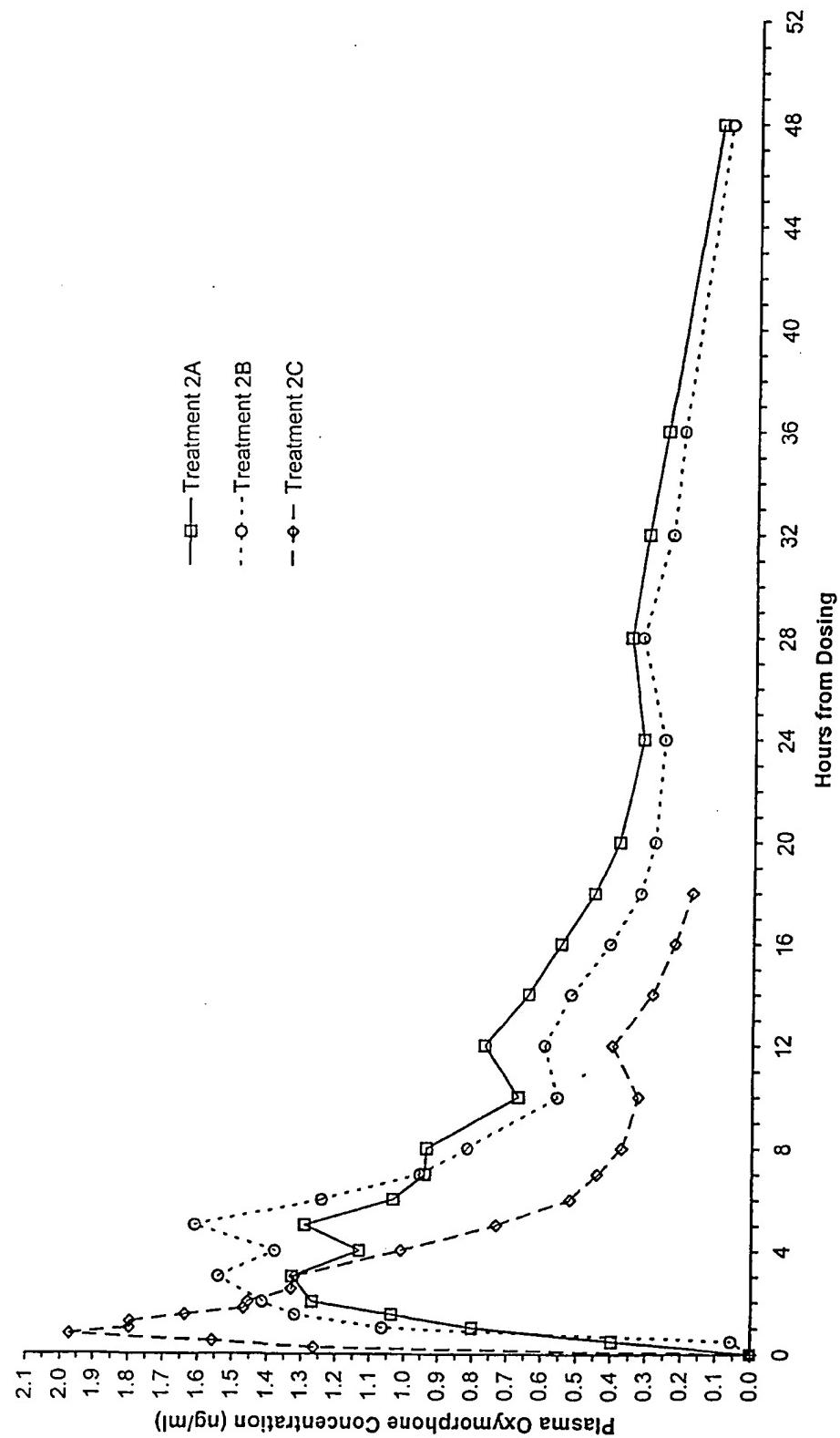


Figure 6

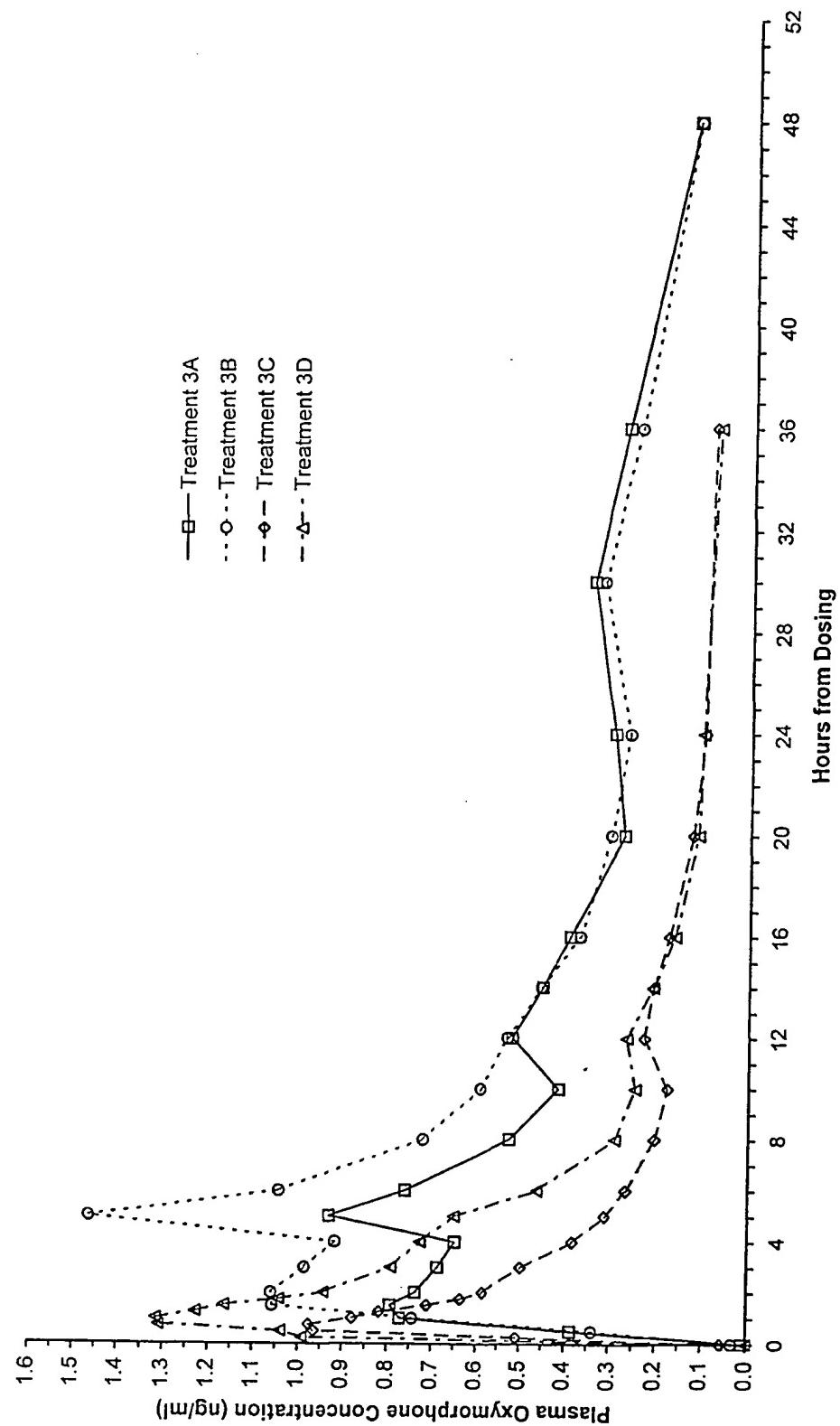


Figure 7

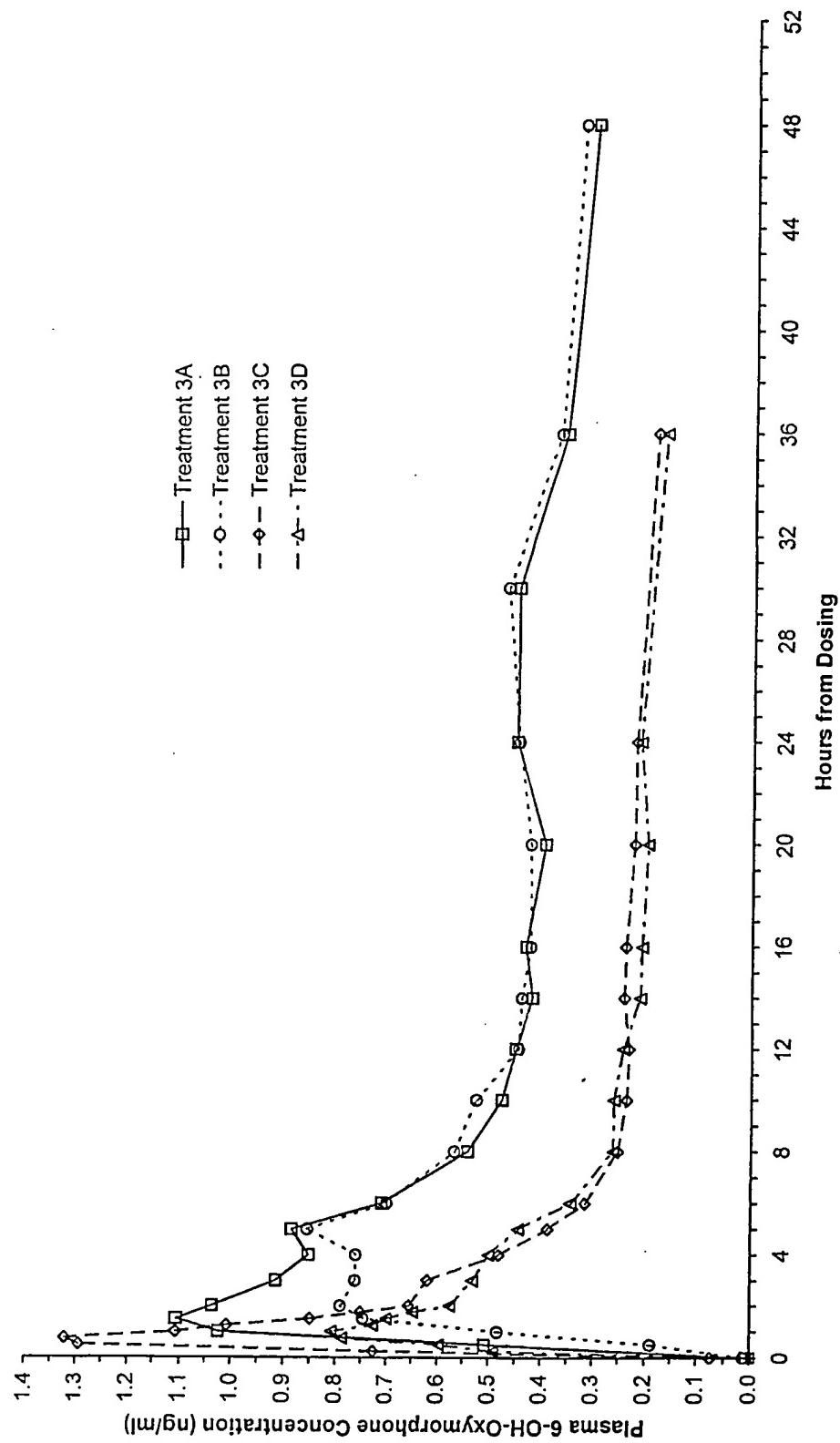


Figure 8

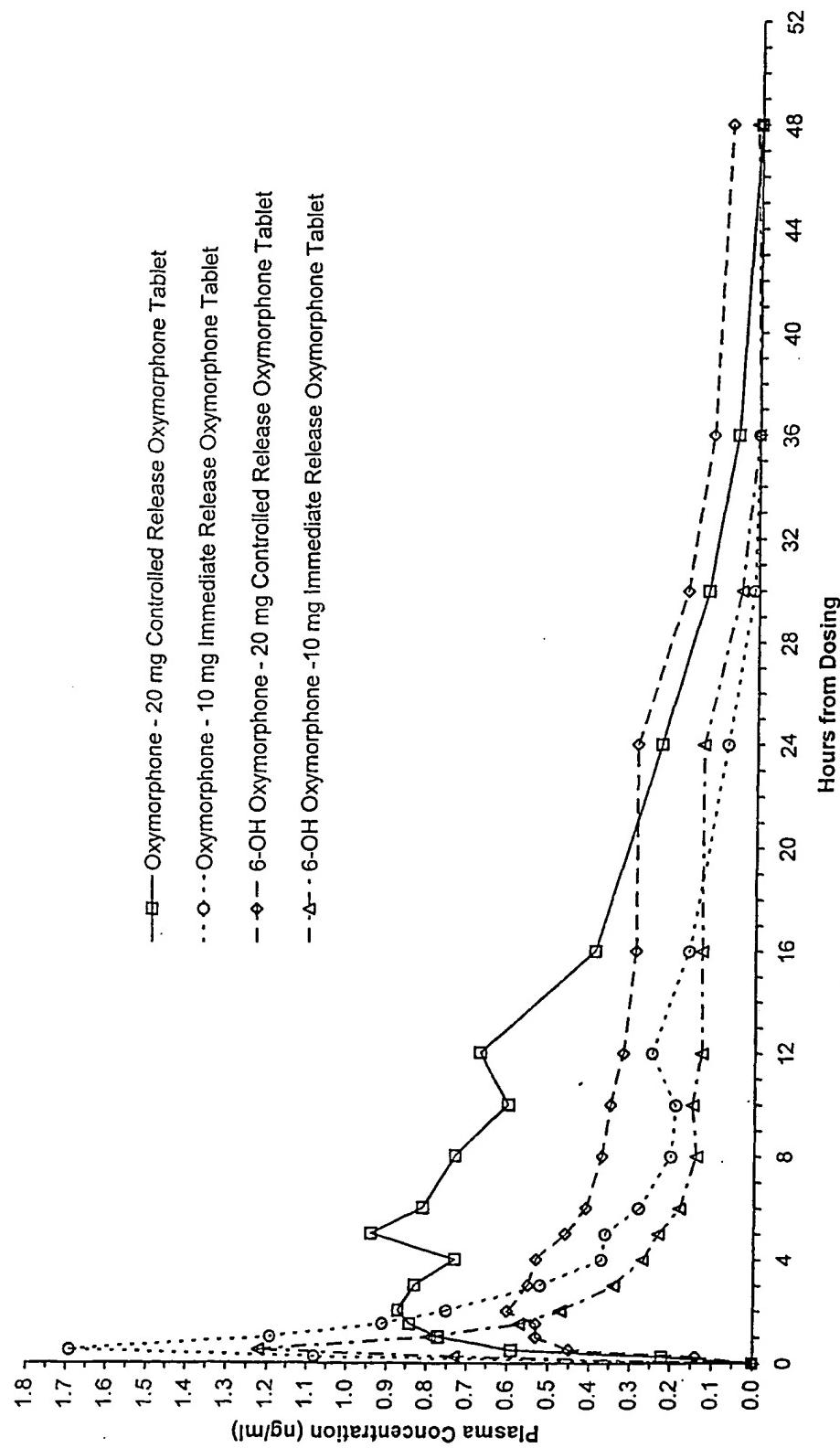


Figure 9

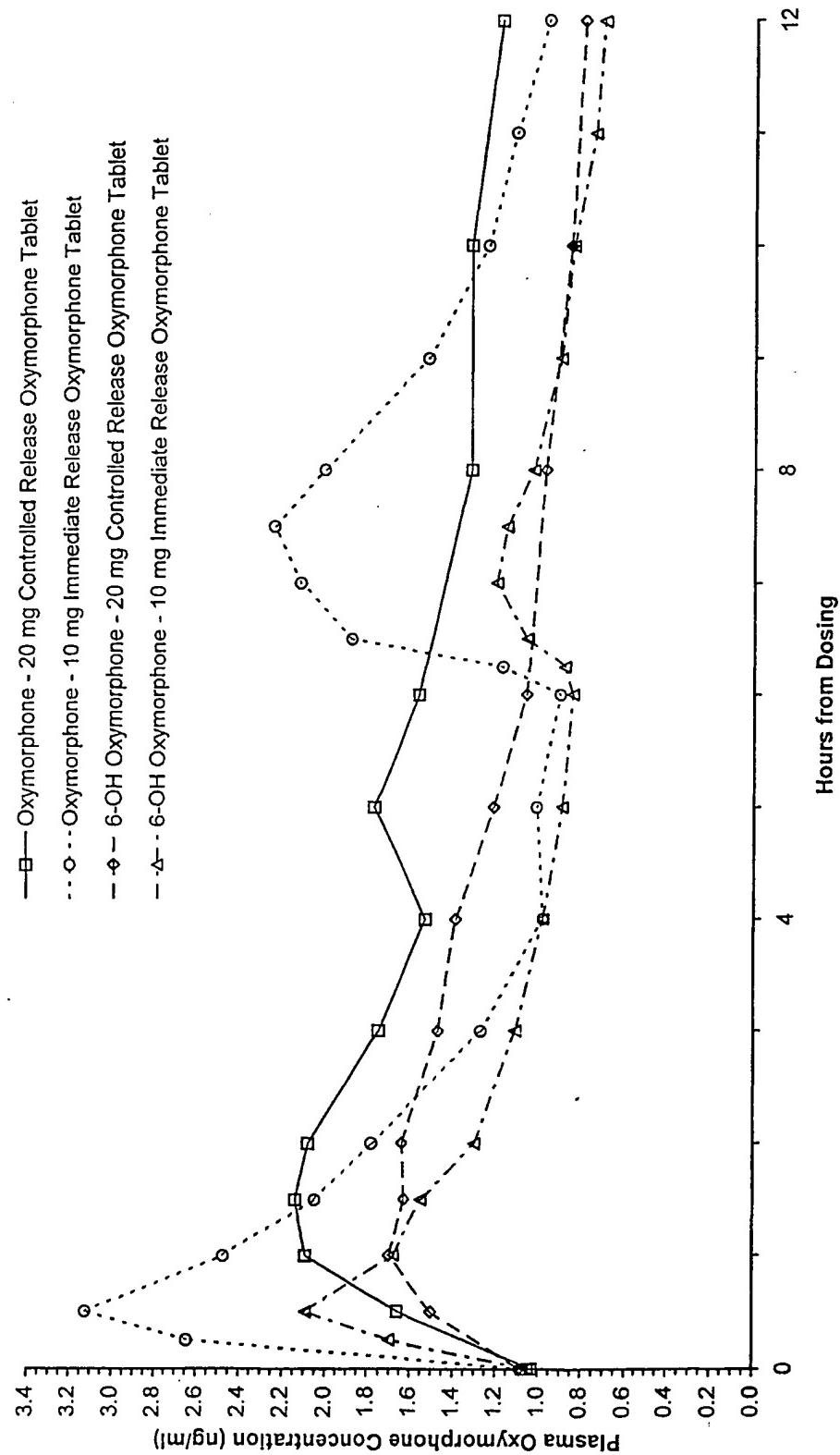


Figure 10

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/21396

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 A61K31/485 A61K9/00 A61P25/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, SCISEARCH, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 08661 A (ROXANE LAB INC) 8 February 2001 (2001-02-08) page 6, last paragraph page 13, paragraph FIRST page 11, paragraph FIRST	1-72, 85-87
Y	---	73-84
Y	US 5 965 161 A (CHASIN MARK ET AL) 12 October 1999 (1999-10-12) column 4, line 65 -column 5, line 28 claim 60	73-84
Y	US 4 366 159 A (MAGRUDER MICHAEL R) 28 December 1982 (1982-12-28) column 2, line 43-56 column 3, line 64-67	73-84

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the International search report
23 October 2002	06/11/2002
Name and mailing address of the ISA  European Patent Office, P.B. 5818 Patenlaan 2 NL - 2280 HV Rijswijk Tel: (+31-70) 340-2040, Tx: 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  Brunnauer, H

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 02/21396

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 73-84 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple Inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the Invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-72 and 85-87 relate to compounds defined by reference to a desirable characteristic or property, namely by means of pharmacokinetic properties.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds as disclosed in examples 2-4 (page 14-15 of the description).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/21396

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 0108661	A	08-02-2001	AU EP WO	6381300 A 1204406 A2 0108661 A2	19-02-2001 15-05-2002 08-02-2001
US 5965161	A	12-10-1999	AU AU AU CA EP HU IL JP JP KR TW WO US US US US ZA	705894 B2 4157096 A 4736299 A 2204180 A1 0785775 A1 77626 A2 115871 A 3186064 B2 10508608 T 232945 B1 425288 B 9614058 A1 2001033865 A1 6261599 B1 2001036476 A1 5958452 A 9509367 A	03-06-1999 31-05-1996 28-10-1999 17-05-1996 30-07-1997 29-06-1998 17-08-1999 11-07-2001 25-08-1998 01-12-1999 11-03-2001 17-05-1996 25-10-2001 17-07-2001 01-11-2001 28-09-1999 13-06-1996
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